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(54) Title: AN OPTIMAL DISSIMILARITY METHOD FOR CHOOSING DISTINCTIVE ITEMS OF INFORMATION FROM A LARGE BODY OF INFORMATION		
(57) Abstract The method of this invention identifies distinctive items of information from a larger body of information on the basis of similarities or dissimilarities among the items and achieves a significant increase in speed as well as the ability to balance the representativeness and diversity among the identified items by applying selection criteria to randomly chosen subsamples of all the information. The method is illustrated with reference to the compound selection requirements of medicinal chemists. Compound selection methods currently available to chemists are based on maximum or minimum dissimilarity selection or on hierarchical clustering. The method of the invention is more general and incorporates maximum and minimum dissimilarity-based selection as special cases. In addition, the number of iterations required to select the items is a multiple of the group size which, at its greatest, is approximately the square root of the population size. Thus, the selection method runs much faster than the methods of the prior art. Further, by adjusting the subsample size parameter K, it is possible to control the balance between representativeness and diversity in the compounds selected. In addition, the method can mimic the distributional properties of selections based on hierarchical clustering and, at least in some cases, improve upon them.		

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AN OPTIMAL DISSIMILARITY METHOD FOR CHOOSING DISTINCTIVE ITEMS OF INFORMATION FROM A LARGE BODY OF INFORMATION

BACKGROUND OF THE INVENTION

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Field of the Invention:

10 A method is presented which identifies distinctive items of information from a larger
body of information on the basis of similarities or dissimilarities among the items. More
specifically, the method achieves a significant increase in speed as well as the ability to
balance the representativeness and diversity among the identified items by applying
selection criteria to randomly chosen subsamples of all the information.

Description of Background Art:

15 Most disciplines from economics to chemistry are benefiting from the ability of the
modern computer to store and retrieve vast amounts of data. While the chore of actually
handling the data has been reduced, the ability to gather, store, and operate with the
enormous amount of data has, in itself, created new problems. In particular, in some cases
20 the amount of data has become so vast that it is difficult to comprehend the range of data,
much less to understand and derive meaningful information from it. To address this
problem, attempts have been made in the prior art to find ways to meaningfully group or
abstract some structure from the information.

For instance, in many situations it is useful to use a stratified sampling procedure
25 for getting aggregate information about a population within which different groups cost
different amounts to survey, or whose response have different meanings to the questioner,
etc. However, while the stratified sampling approach is very efficient, to use it one must be
able to quickly get information about each cluster within the population, and be able to
select representative people to poll. The method of this invention permits the rapid
30 evaluation of the demographic profiles in such a situation to see how many people in a
random sample are "closest" to each selectee. Small, but information profitable target
groups can then be surveyed in this way.

The approach of this invention could also aid in the design of clinical trials. It often happens that drugs tested in a small random sample fail later because of severe adverse reactions in a small subpopulation. Using the method of this invention, a selection based on medical and family history could produce a more useful early phase test population. The following discussion of the method of this invention is presented in terms useful to medicinal chemists who are concerned with identifying subpopulations of chemical compounds. However, as can be seen from the brief examples above, the method of the invention is general and can equally well be applied to other fields by those skilled in the art. The generality of the method is readily appreciated if for the term "compound" used in this disclosure, the term "data element" is substituted. Brief examples of other specific applications of the methodology of the invention are set out at the end of the disclosure.

The advent of combinatorial chemistry and high through-put screening has made the ability to identify "good" subsets in large libraries of compounds very important, whether the libraries in question have actually been synthesized or exist as assemblies of virtual molecular representations in a computer. One kind of a good subset is one which contains members which represent the chemical diversity inherent in the entire library while at the same time not containing more members than are necessary to sample the inherent diversity. This desire for a good subset is driven by the fact that these libraries can contain an enormous number of compounds which, if every single compound were tested, would be extremely costly in terms of money, time, and resources to individually evaluate. Essentially, what is desired is a subset of a size which is reasonable to test. Clearly, good subsets can be generated based upon other criteria as well, such as ease of synthesis or lowest cost. Traditionally such subsets have been created by expert systems - i.e., having a medicinal or pesticide chemist select compounds manually based on a series 2D structures. This approach is labor-intensive and is dependent on the expert used. Moreover, it is neither routinely practical nor very good for more than 300-1000 compounds, and then only when the library in question includes one or more homologous series. In the prior art, currently available alternative approaches for selection include maximum dissimilarity selection, minimum dissimilarity selection, and hierarchical clustering, among others. Each of the available methods can be effective, but each has some intrinsic limitations.

Maximum Dissimilarity: The methods currently most often used for selecting compounds focus on maximizing the diversity of the selected subset with respect to the set as a whole using a descriptor (metric) which characterizes the members of the set and an

associated (dis)similarity measure¹⁻³. The basic approach is straightforward, and utilizes as parameters a minimum acceptable dissimilarity (redundancy) threshold R and a maximum selected subset size M_{max} . The approach is essentially as follows:

1. Select a compound at random from the dataset of interest, add it to the selection subset, and create a pool of candidate compounds out of the remainder of the dataset.
2. Examine the pool of candidates, and, using the characterizing measure (metric), identify the candidate which is most dissimilar to those which have already been selected.
3. Determine whether the dissimilarity of the most dissimilar candidate is less than R (redundancy test). If it is less than R , stop. If it is not less than R , add that candidate to the selection set and remove it from the pool of candidates.
4. If the compound to be selected in this step is the third compound being selected, after its selection return the first two selections to the pool of candidate compounds. (The first selection was chosen randomly, and the second selection is strongly biased by the first. Transferring them back into the candidate pool reduces the effect of the initial random selection.)
5. If the desired subset size M has been reached, stop.
6. If there are no more candidates in the pool, stop. If there are more candidates in the pool, go back to step 2.

A related method developed by Agrafiotis works by comparing evolving subsets to maximize the diversity across the entire set⁴. Maximally diverse subsets are, by definition, biased towards inclusion of outliers; i.e., those candidates most dissimilar from the group as a whole. In some situations, this is very useful property, but medicinal chemists tend to avoid outliers in making their own selections because they may not "look like" drugs. In some cases, outliers in corporate databases are outliers for good reason - difficulty of synthesis or toxicity, for example - which reduces their value as potential leads. Moreover, a maximally diverse subset may not be adequately representative of the biochemical diversity in a dataset.

One justification in drug research for maximizing diversity is based on experimental design considerations commonly employed for analyzing quantitative structure/activity relationships (QSARs),⁵ where outliers are important because they have the greatest weight.

The libraries from which subsets are to be selected are usually much more diverse and much larger in size than those used for QSAR, however. In such a situation, outliers loose their statistical leverage because it may no longer be possible to use the QSAR approach to adequately approximate biochemical responses as linear or quadratic functions of the descriptors (metrics) being used.

Minimum Dissimilarity: Recently, Robert Pearlman *et al.* introduced an alternative approach to compound selection (the "elimination method" in DiverseSolutions⁶) which can be characterized as minimum dissimilarity selection. The approach takes the same two parameters as maximum dissimilarity selection – a minimum dissimilarity threshold R and M_{max} , the maximum number of compounds to select – but applies them differently as follows:

1. Select a compound at random from the dataset of interest, add it to the selection set, and create a pool of candidate compounds out of the remainder of the dataset.
2. Examine the pool of candidates, and, using the characterizing measure (metric), remove any for which the dissimilarity to the most recent selection is less than R .
3. If there are no more candidates in the pool, stop.
4. Select a compound at random from the pool of candidates.
5. If the desired subset size M has been reached, stop.
6. Go back to step 2.

Notice that in each iteration, the similarity test (step 2) is applied only with respect to the most recent compound selected at that iteration. This limits the method to pairwise measures of dissimilarity and can not be used with measures between single compounds and a set of compounds. As Holliday and Willett have pointed out, the definition of set-wise dissimilarity can radically affect the outcome of a dissimilarity-based selection method,³ just as the linkage method used can affect the outcome of hierarchical clustering.^{7,8}

Minimum dissimilarity selection tends to be order dependent¹; i.e., the members included will be dependent on the initial random selections. This can be alleviated by setting M_{max} very high, so that the method runs to exhaustion; i.e., runs out of candidates before M is reached [stops at step 3]. For most datasets, doing so with an empirically justified value for R (e.g., 0.15 – 0.2 for Tanimoto dissimilarity of 2D fingerprints^{9,10}) will return an undesirably large number of selections. Typically, it is necessary to repeat the

minimum dissimilarity selection several times on the same dataset in order to find a value of R which will yield the desired number of selections when minimum dissimilarity is run to exhaustion. If a reasonable value of M_{max} and a neighborhood¹⁰ radius R are used, the minimum dissimilarity method will return a subset similar to one chosen by random selection, where the only difference is that there will be no redundant selections, as defined by R . Such a selection will be representative but may not be diverse enough to satisfy some chemists.

Hierarchical Clustering: In agglomerative hierarchical clustering, the most similar pair of clusters are consolidated at each level, starting from one singleton cluster for each compound in the set. Selecting from clusters obtained using Ward's or complete-linkage methods^{1,8} returns subsets which are both representative and diverse, in that each compound is represented by some neighbor and the representatives are distributed across the full breadth of the dataset. Medicinal chemists generally find selections based on hierarchical clustering intuitively appealing and natural, especially after they have eliminated "oddball" clusters and singleton compounds from the selection list. Indeed, they sometimes make their own selections by manually clustering structures. By examining the dissimilarity between the most similar clusters at each step, one can identify the most "natural" level of clustering near the number of compounds one wishes to select - i.e., levels at which the last clusters consolidated were substantially more similar than any remaining clusters are to each other.

Hierarchical clustering is not always a practical option, however. The speed of the classical technique decreases with the cube of the size N of the dataset,^{1,8} and so becomes slow for large libraries. In addition, computer memory requirements generally restrict direct applications to relatively small datasets (≤ 2000 compounds). Faster approaches, including reciprocal nearest neighbors (RNN),⁸ are available which relieve the memory limitations and can usually reduce scaling problems dramatically.¹ However, even in the best case, the speed is inversely proportional to N^2 . Unfortunately, the scaling benefits can only be fully realized when centroids are well-defined and well-behaved in the metric space being explored, which is not the case for some important metrics of interest - in particular, for Tanimoto similarities between 2D fingerprints.^{9,10}

Definitions:

N shall mean the entire set of elements contained in a dataset from which it is desired to select a subset.

M shall mean the size of the subset of elements which it is desired to select.

R shall mean an exclusion criterion chosen by the user. One example of such a criterion is a minimum dissimilarity threshold between the data elements.

K shall mean a subsample size chosen by the user.

SUMMARY OF THE INVENTION

The method of this invention addresses the problem of how to select from a very large dataset of information, a smaller subset for detailed analysis and/or evaluation which reflects the full range of information contained in the large dataset. The present method significantly improves on the methods available in the prior art in two significant ways.

10 First, it is possible to adjust the balance for a data subset between how representative the selected subset is and how diverse it is. Second, the method achieves the desired selection much faster than any comparable method. In particular, while the number of fundamental steps to obtain a subset of a given size in prior art methods are multiples of the size of the dataset N or powers of N^2 , it has been discovered that, with the method of this invention,
15 the number of steps required is a multiple of M which, at its greatest, is approximately the square root of N , \sqrt{N} .

In prior art selection methods large datasets are examined as a whole. In the method of this invention a subsample K of the entire dataset size N is defined and examined. The method of this invention is more general than those of the prior art, and, in fact, reduces as
20 limiting cases to the minimum and maximum dissimilarity methods of the prior art for values of $K = 1$ and $K = N$. The tradeoff between how representative or how diverse the selected subset is may be varied by the user by selecting intermediate values of K .

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 diagrammatically shows the compounds chosen at each of the first three
25 iterations of a selection performed by the method of this invention ($R = 6\text{mm}$ (original scale), $K = 5$, $M_{\text{max}} \geq 3$). Symbols representing compounds which have already been selected are filled in solid. The circles around each solid symbol show the minimum dissimilarity radius R ; dark hash symbols indicate compounds examined at each iteration which are excluded as too similar to those which have already been selected. Stippled
30 symbols indicate candidates in the recycling bin, i.e., which have already been considered for selection once.

Figure 2 shows the design of the parent libraries contributing to the combinatorial dataset

Figure 3 shows the distribution of scalar descriptors for the combinatorial dataset. (A) Data for all 1000 compounds is displayed in three dimensions. (B) Distribution for 150 compounds in the XY plane.

Figure 4 shows the relationships among compound classes in the combinatorial dataset as shown by hierarchical clustering on UNITY 2D fingerprints.¹³

Figure 5 shows the divergence of OptiSim selections from uniform sampling across pharmacological classes for the Mannhold-Rekker dataset¹⁷ as a function of subsample size K . The χ^2 statistic is scaled by division by its 5 degrees of freedom.

Figure 6A shows the relationship between the average dissimilarity ρ between unselected compounds and sets of 21 compounds selected by OptiSim as a function of the average dissimilarity δ among selected compounds. One of two sets of 100 compounds randomly selected from the combinatorial dataset was used to calculate ρ for each trial. The data shown is for UNITY 2D fingerprints from the combinatorial dataset. (\bullet) $K = 1$; (\circ) $K = 2$; (\blacksquare) $K = 5$; (\square) $K = 10$; (\blacklozenge) $K = 15$; (\diamond) $K = 25$; (\blacktriangle) $K = 35$; (∇) $K = 1000$; (—) spline curve drawn through the mean values of ρ and δ for each value of K .

Figure 6B shows the relationship between the average dissimilarity ρ between unselected compounds and sets of 21 compounds selected by hierarchical clustering as a function of the average dissimilarity δ among selected compounds. (\blacksquare , \square) selections made from hierarchical complete linkage clusters⁸; (\blacktriangle , ∇) selections made from hierarchical group average clusters⁸; (\square , ∇) one compound was randomly selected from each cluster; (\blacksquare , \blacktriangle) one compound was randomly selected from among the three most central compounds in each cluster; (—) spline curve corresponding to that shown for Optisim selections in Figure 6A.

Figure 7 is a diagrammatic flow sheet of the invention.

Figure 8 shows the dendrograms produced by using single linkage, group average, and complete linkage hierarchical clustering to select 30 compounds.

Figure 9 shows dendrograms analogous to those of Figure 8 for Optisim selections made with $K = 1, 3$, and 5. The complete linkage dendrogram from Figure 8 is repeated for comparison.

Figure 10 shows a schematic dendrogram for an Optisim clustering from a selection set of 10 compounds.

Figure 11 is a plot of the distribution of cluster sizes obtained from the test data set for single, group, and complete linkage. The bar codings are the same as shown in Figure

8.

Figures 12 and 13 show the comparison of the cluster size distributions obtained from Optimis clusterings based on $K = 1, 2, 3$, and 5 to the complete linkage clustering. The bar codings are the same as shown in Figure 8.

5

DESCRIPTION OF THE PREFERRED EMBODIMENT

Holliday and Willett have pointed out³ that their own¹¹ and other² dissimilarity-based selection methods were actually specific manifestations of a more general, unified method, and in particular, they addressed the question of what similarity meant when comparing one compound to a group of compounds. Lance and Williams⁷ have done much the same analysis for hierarchical clustering. In a similar way, maximum and minimum dissimilarity selection can be reformulated as limiting cases of a single, more general method, the "OptiSim" method of this invention. The generalization entails introduction of a parameter K which defines a subsample size at each iteration. The method can be outlined as follows:

1. Select a compound at random from the dataset of interest, add it to the selection set, and create a pool of candidate compounds out of the remainder of the dataset. Create an empty recycling bin.
2. Randomly select a subsample set of K compounds (or all remaining) from the candidate pool. If necessary, transfer compounds from the recycling bin to the candidate pool and randomly select a sufficient number of compounds (if possible) to complete a subsample of size K .
3. Determine whether any of the compounds in the subsample set have a dissimilarity less than R with respect to those compounds already selected. (In the case of the first pass, this will only be the initially randomly selected compound.) Remove any such compounds from the subsample and replace them with other compounds from the candidate pool.
4. If the candidate pool is exhausted, remove all compounds from the recycling bin and put them back into the candidate pool.
5. Repeat step 3 until the subsample includes K compounds at least R dissimilar to those already selected or until the candidate pool is exhausted.
6. If the subsample is empty, stop.
7. If the subsample is not empty, examine the subsample, and identify a compound maximally dissimilar to those already selected.
8. Add the compound identified in step 7 to the selection set and remove it

from the subsample.

9. Put those compounds in the subsample which were not selected into the recycling bin.
10. If the desired selected subset size M has been reached, stop. If the desired selected subset size M has not been reached, return to step 2.

A preferred alternative formulation of the method can be set out as follows:

1. Select a compound at random from the dataset of interest, add it to the selection set, and create a pool of candidate compounds out of the remainder of the dataset. Create an empty recycling bin.
2. Randomly choose another compound from the dataset and determine if it has a dissimilarity less than R with respect to those compounds already selected for the selection set. If it does not have a dissimilarity less than R , place it in the subsample.
3. Repeat step 2 until the subsample includes K compounds at least R dissimilar to those already selected or until the candidate pool is exhausted.
4. If the candidate pool is exhausted but the recycling bin is not exhausted, remove all compounds from the recycling bin and put them back into the candidate pool.
5. If the candidate pool is not exhausted and there are fewer than K compounds in the subsample, go to step 2.
6. If the subsample is empty, stop.
7. If the subsample is not empty, examine the subsample and identify a compound maximally dissimilar to those already selected.
8. Add the compound identified in step 7 to the selection set and remove it from the subsample.
9. Put those compounds in the subsample, which were not added to the selection set, into the recycling bin.
10. If the desired selected subset size M has been reached, stop. If the desired selected subset size M has not been reached, return to step 2.

Figure 7 shows the method of this invention set out in flowsheet format.

The results of the application of the first formulation of the method for three iterations are illustrated schematically in Figure 1, where filled in symbols indicate selected compounds.

Clearly, the maximum and minimum dissimilarity selection methods can be seen simply as extreme instances of this *Optimal Dissimilarity Selection* approach¹² - OptiSim, for short. For maximum dissimilarity, K is effectively N , the number of elements in the dataset: all compounds are considered as candidates at each step. The only substantive
5 difference from the prior art maximum similarity method is that the first two selections are not dropped (step 4 in the maximum dissimilarity approach), so the selections obtained are slightly more representative and less diverse than would be the case for the original method.

For minimum dissimilarity, K is simply 1. In addition, the similarity test (step 3) is
10 applied to each candidate with respect to all elements which have already been selected. This method broadens the range of dissimilarity measures which can be used over the version of the minimum dissimilarity method described above.

An important aspect of the present invention is that, by choosing an intermediate value of K , it is possible to strike a balance along the continuum between the diversity of
15 the maximum dissimilarity approach and the representativeness of the minimum dissimilarity approach. As shown below, it turns out that one can mimic selection based on hierarchical clustering as well. Thus, the method of this invention is more general than prior art approaches and, when desired, reduces to or mimics the prior art approaches.

Experimental Methodology: Combinatorial dataset design.

20 Generally, all calculations and analyses to conduct combinatorial chemistry screening library design and follow up are implemented in a modern computational chemistry environment using software designed to handle molecular structures and associated properties and operations. For purposes of this Application, such an environment is specifically referenced. In particular, the computational environment and capabilities of
25 the *SYBYL* and *UNITY* software programs developed and marketed by Tripos, Inc. (St. Louis, Missouri) are specifically utilized. Unless otherwise noted, all software references and commands in the following text are references to functionalities contained in the *SYBYL* and *UNITY* software programs. Software with similar functionalities to *SYBYL* and *UNITY* are available from other sources, both commercial and non-commercial, well known to
30 those in the art. A general purpose programmable digital computer with ample amounts of memory and hard disk storage is required for the implementation of this invention. In performing the methods of this invention, representations of thousands of molecules and molecular structures as well as other data may need to be stored simultaneously in the

random access memory of the computer or in rapidly available permanent storage. The inventors use a Silicon Graphics, Inc. *Challenge-M* computer having a single 150Mhz R4400 processor with 128 Mb memory and 4Gb hard disk storage space. SPL (Sylbyl Programming Language) code to implement a preferred method of this invention is set forth in Appendix "A".

The Legion¹³ combinatorial builder module in SYBYL¹³ was used to create a homologous set of libraries, each with a pyrimidine, a cyclohexane or a pyridine at the core (Figure 2) and an analogous pattern of substitution around each ring. The pyrimidine and cyclohexane libraries consisted of 2244 compounds each, whereas the pyridine library was made up of 6000 compounds. A composite library was built from the 6000-compound pyridine dataset, 500 randomly selected cyclohexanes and 100 randomly selected pyrimidines. The final dataset of 1000 compounds - 892 pyridines, 92 cyclohexanes and 16 pyrimidines - was created by randomly selecting from among the 6600 compounds in the composite library. The Tanimoto dissimilarity T* (equivalent to the Soergel distance^{14,15}) was used to assess the dissimilarity between any two compounds a and b in the dataset:

$$T^* = 1 - \frac{\text{No. Of Bits Occuring } \in \text{ Both Molecules}}{\text{No. Of Bits } \in \text{ Either Molecule}}$$

The Tanimoto fingerprint simply expresses the degree to which the substructures found in both compounds is a large fraction of the total substructures. Standard UNITY¹³ 2D fingerprints were used for evaluating dissimilarities.

Three scalar descriptors were generated for the combinatorial dataset by drawing three numbers for each compound from a uniform random population of reals between 0 and 1, then squaring each number and multiplying it by 99. Adding 1 to the integer part of each value produced three descriptors for each compound with values between 0 and 100. These were distributed independently of the 2D structure and, hence, of the corresponding fingerprints. The distribution of values in the resulting scalar three-descriptor space forms a gradient of density running out from the concentration of points near the origin (Figure 3). Dissimilarity was evaluated in terms of Euclidean distance when using these descriptors to evaluate the performance of OptiSim on multiple scalar descriptors.

χ^2 comparisons: Subsets generated by Optimal Dissimilarity Selection at various subsampling levels K were characterized non-parametrically in terms of the χ^2 statistic: where O_i denotes the observed count obtained from the i^{th} of c clusters and E_i denotes the

$$\chi^2 = \sum (O_i - E_i)^2 / E_i$$

count expected from that cluster¹⁶ (the term "cluster" is used here because the comparisons of most immediate interest are between cluster-based selection and OptiSim results; "category" or "class" would be equally appropriate).

The χ^2 statistic with respect to a random sample is a measure of how representative a particular selection set is. In general, the expected count for random sampling is given by:

$$E_i(\text{random}) = b M n_i / N$$

where b is the number of trials in each block; M is the number selected per trial; n_i is the number of compounds in the i^{th} cluster; and N is the total number of entities being selected from. For random sampling, one expects to select most often from the most populous cluster, and to select proportionately less often from smaller clusters. The larger a selection set's value of $\chi^2(\text{random})$, the more it diverges from being representative of the dataset as a whole.

Note that the OptiSim method of this invention explicitly precludes re-selecting any compound, whereas the random selection distribution is for sampling with replacement. As a result, the selections are not strictly independent of each other and (2) is not exact. This is not a problem if the number of selections per trial does not greatly exceed the number of clusters. It is then necessary, however, to block trials if one is to keep the expected number of selections for each cluster large enough to avoid having to make a continuity correction to the χ^2 statistic calculated in (1).¹⁶

If selection is perfectly uniform across clusters, each cluster will be equally likely to be sampled. How uniformly a selection is distributed across c clusters, then, is a measure of how similar a result is to cluster-based selection. The $\chi^2(\text{uniform})$ statistic is therefore calculated from:

$$E_i(\text{uniform}) = b M / c$$

Again, perfect concordance gives a χ^2 of 0. The smaller $\chi^2(\text{uniform})$ is, the better the result mimics cluster-based selection.

Scaling: As noted above, a perfectly random selection will have a $\chi^2(\text{random})$ of 0, and a perfectly uniform selection will have a $\chi^2(\text{uniform})$ of 0. Both results, however, are quite unlikely when selections are made independently. For either statistic, the mean χ^2 expected by chance is equal to the degrees of freedom ($df = c - 1$). Scaling by this

population mean makes it easier to compare experiments which involve different numbers of clusters (i.e., categories of classification), since it makes the expected result equal to 1 no matter how many clusters are involved.

Experimental Results - Power of Optimism Methodology:

5 Scalar descriptors: A hierarchical clustering was done in Selector¹³ using complete linkage on the three scalar descriptors generated for the 1000 compounds in the combinatorial dataset, which resolved the dataset into ten clusters. Two clusters split one corner of the cubical descriptor space; the rest cover the remaining corners and the center. The ten clusters obtained were made up of 283, 167, 134, 130, 90, 78, 45, 29, 24 and 20
10 compounds, respectively. Not surprisingly, the largest cluster is near the origin and the smallest is at the opposite vertex of the cubical boundaries of the descriptor space.

Optimal Dissimilarity Selection was then applied to the dataset 20 times at each of seven different subsampling rates K , selecting ten compounds ($M_{max} = 10$) each time; R was set to 10. The same random number was used to "seed" the method for one trial at
15 each subsampling rate, so any biases due to the initial selection were spread equally across all values of K . The number of selections from each cluster was summed across a block of ten such trials, so that each block included 100 selections for each subsample size. The χ^2 statistics obtained were then averaged across two such blocks. The total number of scalar selections was therefore:

20 $(10/\text{trial}) \times (10 \text{ trials/block}) \times (2 \text{ blocks}) \times (7 \text{ subsampling rates}) = 1400$
in 140 trials, with a total of 200 selections made for each subsampling rate.

The distributions of these selections across clusters were then compared to the totals expected for random sampling and to the totals expected for uniform selection from the ten clusters. Table 1 shows the χ^2 values obtained as averages across two blocks for each value
25 of K .

Table 1

Divergence of subsets selected from the combinatorial dataset from random and uniform distributions across clusters. Values cited are in terms of scaled chi squared (χ^2 /degrees of freedom).

5	K^a	scalars (df=9)		fingerprints (df=20)	
		random ^b	uniform	random	uniform
	1	1.23±0.43 ^c	7.21±0.14	0.89	15.05
	5	2.06±0.50	3.56±0.51	4.04	7.36
	10	2.58±0.11	2.44±0.11	11.15	5.56
10	15	5.04±0.66	1.98±0.24	13.75	3.94
	25	5.88±1.16	1.93±0.38	20.32	3.38
	35	7.61±2.89	2.02±0.07	26.74	2.08
	1000 ^d	7.59±0.72	0.67±0.15	49.84	2.05

15 a Subsampling rate at each iteration.

b Reference distribution.

c Mean± SEM for two blocks.

d All unselected compounds considered at each iteration.

The χ^2 (random) for minimal dissimilarity selection ($K = 1$) is not significantly
 20 different from that expected by chance (1.23 vs 1.0), but it rises steadily with increasing K
 as the selected subsets grow more diverse and less representative. The χ^2 (uniform) profile, on
 the other hand, falls quickly with increasing K to a plateau value of about 2 for $K = 15-35$.
 The maximal dissimilarity extreme ($K = 1000$) produces a significantly more uniform
 distribution (0.67 vs ~2.0), which reflects the fact that a cluster is, in this case, located at
 25 each of the first nine linear D-optimal points of the descriptor space – the corners plus the
 center.

Note: maximum dissimilarity selection ($K = 1000$) performs unusually well here with
 respect to hierarchical clustering in part because the dimensionality (3) is much smaller than
 M_{max} (10), and in part because the peak population density near the origin coincides with one
 30 extreme of the descriptor space.

Combinatorial fingerprints: Hierarchical clustering of the combinatorial dataset using

2D fingerprints gave 21 clusters as a "natural" level (see discussion above of hierarchical clustering). These included 19 "pure" clusters made up of 262, 152, 75, 64, 64, 45, 43 or 17 pyridines; 29, 21, 11, 10, 6, 5, 5, 3 or 2 cyclohexanes; and 8 or 2 pyrimidines. Two mixed clusters contained both pyridines and pyrimidines - 161 and 2, or 9 and 4, respectively. The relationships between the sublibraries shown by this clustering pattern are illustrated schematically in Figure 4. Note that the areas of each set shown in Figure 4 indicate the number of compounds of that class which are in the dataset, not the degree of diversity within each class. Because they are drawn from homologous combinatorial libraries, the degree of structural variety found within each class is similar. This is reflected in the similar numbers of pyrimidine and cyclohexane clusters; that fewer pyrimidine clusters were identified simply reflects their scarcity.

Twenty-one compounds were selected in each trial ($M_{max} = 21$), and distributions across clusters were summed across 10 trials for each block at each of seven values of K ; R was set to 0.15.^{9,10} Again, there was one trial at each subsampling rate for each random number seed used; the seeds used were different from those used for analyzing the associated scalar descriptors. In this case, blocks were not replicated. Hence the total number of trials was:

$$(21/\text{trial}) \times (10 \text{ trials/block}) \times (7 \text{ subsampling rates}) = 1470$$

in 70 trials, with a total of 210 selections made at each of 7 values of K .

The values of scaled χ^2 found with respect to random and uniform distributions are shown in Table 1. Again, the OptiSim selections move away from being purely representative and begin to resemble cluster-based selection even at low values of K . Note that under this high-dimensional, non-Euclidean metric the limiting scaled χ^2 (uniform) is 2.0.

Again, maximum dissimilarity ($K = 1000$) returned the most uniformly distributed selection set. Note, however, that the number of superclusters (3 - one for each of the constituent combinatorial core structures) is small compared to M_{max} (here, 23). The distribution of compounds chosen using maximum dissimilarity selection can be uncharacteristically uniform in such a situation.

Mannhold-Rekker dataset: The combinatorial dataset described above is very structured and artificial. It was created so deliberately in an effort to keep evaluation of the selection method - OptiSim - separate from the considerations of the appropriateness of the particular metric being used. Nonetheless, it is important to know how well the methodology performs with more realistic datasets. Mannhold *et al.*¹⁷ compiled a database of 68 structurally diverse

compounds from six pharmacological classes for evaluating different ways of predicting a compound's octanol/water partition coefficient P from its structure. The dataset includes 15 class I antiarrhythmics, 13 phenothiazines, 12 class III antiarrhythmics, 11 β -blockers, 9 benzamides and 8 potassium channel openers. OptiSim was used to select six compounds from the dataset in nine trials with K set to 1, 3, 5, 7, 10 or 68. Again, standard UNITY 2D fingerprints were used to evaluate the dissimilarity between molecules.

In this case, the uniform reference distribution was based on pharmacological classes. Because there is relatively little variation in population between classes in this dataset, however, the analysis applied above to the combinatorial dataset is not very informative, particularly *vis à vis* random sampling. Instead, χ^2 (uniform) was calculated for each trial, and the results averaged across the nine trials for each subsampling rate K . The results obtained are shown in Figure 5; selection of one example from each pharmacological class was best reproduced at $K = 5 - 7$.

Note that here, where the underlying complexity of the dataset (6) is comparable to M_{max} , intermediate values of K outperform maximum dissimilarity. In fact, OptiSim actually performs somewhat better with respect to the pharmacological classes in this dataset than does cluster-based selection based on 2D fingerprints and complete-linkage (data not shown), in part because the variation in structures within classes is uneven.

Parametric measures of diversity and of representativeness: The χ^2 statistic is a good measure of similarity for validation work, but it requires a reference distribution and so is of limited usefulness when no hierarchical classification is available for comparison. If Optimal Dissimilarity Selection is to be used as a surrogate for hierarchical clustering, more readily accessible measures will be needed to know when the optimal balance between representativeness and diversity has been obtained for a given subsample size in any particular application.

It is convenient to use averages when characterizing large datasets, because the law of large numbers guarantees that a good estimate of the average can usually be obtained from a random sample of the entire dataset.¹⁸ If S is the set of M compounds selected and U is the set of n compounds chosen randomly from among those compounds which were not selected, then the average dissimilarity δ between each compound in S and the other compounds in S is a measure of diversity, whereas the average dissimilarity ρ between compounds in S and those in U is a measure of representativeness. The minimum pairwise dissimilarity criterion^{2,3} for

evaluating the dissimilarity between each compound and the reference set is being used, so:

$$\delta = (1/M) \sum_{i=1}^M \min(T^*(s_i, s_j) : 1 \leq j \leq M, i \neq j)$$

$$\rho = (1/n) \sum_{i=1}^n \min(T^*(u_i, s_j) : 1 \leq j \leq M)$$

Figure 6A shows a plot of ρ as a function of δ for fingerprints from the combinatorial dataset; for clarity, only five trials at each of seven levels of subsample size K are shown. Data are also shown in Figure 6B for both unbiased random selection of one compound from each of the hierarchical clusters described above (labelled "random" in Figure 6B), and for random samplings from among the three most central compounds in each cluster¹⁹ (labelled "central" in Figure 6B; this is a Tanimoto space, so "central" compounds are not necessarily representative). Results from both complete linkage and group average hierarchical clustering are shown.

The scatter in ρ and δ among selection sets obtained at the same value of K reflects the random sampling component of the method. The variance in δ falls sharply as K increases, with a standard deviation (SD) of 0.043, 0.012 and 0.010 at $K = 1, 5$ and 35, respectively. For any particular dataset and a given M_{\max} , there is a characteristic limiting value for δ . In this case, δ_{\max} is slightly less than 0.7.

The variance in ρ , on the other hand, is primarily determined by the randomly chosen unselected compounds (U) to which the selection sets are compared, and so decreases only slightly with increasing K . Note that for OptiSim selection sets, ρ and δ will both be smallest (on average) when $K = 1$. Moreover, the expected values for ρ and δ will be equal if and only if: S and U are the same size; $R = 0$; and $K = 1$.

As expected, an increase in diversity (δ) comes at the cost of a decrease in representativeness (increase in ρ). Also as expected, minimum dissimilarity selection ($K = 1$) returns a selection set more representative (lower ρ) but less diverse (lower δ) than does cluster-based selection. Maximum dissimilarity selection ($K = 1000$) increases diversity at some cost in representativeness, particularly with respect to selection from among the central compounds in each cluster (C).

subsampling rates, OptiSim returns selection sets which are both more representative (lower ρ) and more diverse (higher δ) than are the cluster-based selections. This difference in the *quality* of the selections made accounts for the failure of χ^2 (uniform) to fall much below 2 for this dataset when hierarchical clustering is taken as the reference distribution.

5 Recall that the hierarchical clustering used as a reference is based on complete linkage.⁸ Ward's method is an alternative approach which uses a probabilistic, least-squares rationale to maximize distances between clusters while minimizing distances within clusters under Euclidean metrics.²⁰ Evidently, Optisim's sampling approach imparts similar properties to its selection sets. This is potentially a quite useful generalization, since Ward's method is not
10 applicable to metric spaces in which centroids of clusters are not well-defined - in particular, it is not directly applicable to Tanimoto coefficients based on 2D fingerprints or other bit set descriptors.

It has been determined by applying the method of this invention through extensive testing, that there is little or no advantage in selecting a value of K greater than the square root
15 of N . For instance, it can be seen in Figure 5 that the scaled χ^2 has a minimum (~ 5) for a $K < \sqrt{68}$. In addition, in Figure 6A, it can be seen that most of the diversity (δ) obtainable (as indicated by $K = N$, 1000) is achieved with a $K = 35$, approximately the square root of 1000. Also, by the time K is as large as \sqrt{N} , it can be seen that (ρ) representativeness is being
20 lost (ρ higher value) indicating, perhaps, that in this example $K = \sqrt{N}$ may already be too high. Thus, the fundamental number of steps for the method of this invention is proportional to or less than \sqrt{N} .

The ρ vs δ plot such as in Figure 6A is one way to compare different selection sets. Another way is to apply hierarchical clustering to the selection sets themselves. It is then possible to compare the dendrograms produced by such analyses to qualitatively assess the
25 similarities and differences between the selection sets. This is illustrated for single linkage, group average, and complete linkage hierarchical clustering methods in Figure 8. The 1000 compound mixed dataset was partitioned into 30 clusters for each method, and a representative compound was drawn from among the three most central compounds in each cluster. Those representations were then themselves clustered to give the dendrograms shown in Figure 8. For
30 the sake of consistency, this secondary clustering was done using complete linkage in each case. The class of compounds making up each cluster is indicated at the base of the dendrogram, where each vertical line corresponds to the selected representative from one

Based on the dendrograms and on the relative number of pyrimidine and pyridine structures selected, it is clear that the single linkage is the most biased towards unusual structures (pyrimidines) and so gives the most diverse, but least representative selection. Indeed, many of the single linkage clusters are pyrimidine singletons, and the 90% of the dataset comprised of pyridines are lumped together into just seven large clusters. Complete linkage clustering, on the other hand, is skewed towards a better representation of the more common class of compounds (pyridines) and is correspondingly less diverse. Group average clustering provides an intermediate balance in discrimination among and between classes.

Figure 9 shows analogous dendrograms to those of Figure 8 but obtained using the Optimisim method with $K = 1$ (minimum dissimilarity), $K = 3$, and $K = 5$. At the smallest subsample size ($K = 1$), the selection is almost purely representative, with only one pyrimidine and two cyclohexanes being selected. This reflects their numerical contributions to the dataset (2% and 9% respectively) reasonably well. As expected from the ρ vs δ plot of Figures 6A and 6B, the complete linkage selection is mimicked reasonably well by the $K = 5$ selection set. This comparison illustrates another aspect of the similarity between the Optimisim methodology and cluster based selection.

Variations and Extensions Of The Basic Optimisim Methodology:

The heart of the Optimal Dissimilarity Selection approach lies in taking a series of random subsamples from a dataset, and selecting the best candidate from each subsample, where "best" is defined by some preference criterion which is a function of those compounds (or, more generally, elements) which have been selected in previous steps. Several useful variations on the method disclosed in this document will be immediately apparent to those skilled in the art. The following variations as well as others enabled by the disclosure in this document are considered within the scope of this disclosure.

Other evaluation criteria: OptiSim has been defined here solely in terms of maximum minimum pairwise dissimilarity to those compounds already selected as the criterion by which the "best" compound is to be selected from each subsample. The highest average dissimilarity³ could just as well be used, and the cosine coefficient¹¹ could be substituted for the Tanimoto coefficient. In fact, the method is generalizable to any set of selection criteria or decision rules – best priced or most synthetically accessible compound, for example, or lowest price in the highest quartile in dissimilarity. The redundancy test against R can also be defined more broadly:

Similarly, selection for each subsample need not be random, but can be systematically

biased towards compounds in combinatorial libraries which share reagent "parents" with compounds which have already been selected. An analogous scheme is currently implemented in DiverseSolutions⁶ for descriptors of low dimensionality in a cell-based selection system.

Sampling with replacement: As set out in Figure 1, each OptiSim subsample is drawn from the candidate pool for consideration, then is set aside until all candidates have been examined once - i.e., the dataset is sampled without replacement. If samples are drawn with replacement of those compounds which do not get selected, no recycling bin is required. A given setting of K will then return a more representative but less diverse subset because sampling of more sparsely populated (outlier) regions will be avoided. The tradeoff will be that a particular level of diversity among the compounds selected will only be approached at higher values of K , which can become computationally expensive.

Replacement of redundant compounds in the subsample: The implementation described in Figure 1 tests each compound in the subsample for redundancy, and replaces any redundant compounds in the subsample before selecting the best one in that subsample. An alternative approach is to apply the redundancy test only to that best compound; if it is redundant - that is, if it is too similar to those which have already been selected - no selection from that subset is made. This approach can be made faster "up front" than the version of OptiSim set out in Figure 1 for some descriptors and similarity measures, but will be correspondingly slower at later selection steps. In addition, the balance between representativeness and diversity will be shifted towards making more representative selections, just as subsampling with replacement will.

Dataset clustering: As demonstrated here, OptiSim selection sets behave very much like selection sets based on hierarchical clustering. OptiSim selections can be used as centers (i.e., as leaders¹) for efficiently clustering large datasets on the basis of a secondary similarity radius, R' , or by assignment of each compound to the most similar center. Moreover, selected compounds can themselves be submitted to hierarchical clustering. Under this scenario, the OptiSim selections will be true centers of their R' neighborhoods¹⁰ for any metric, so their hierarchy will perforce accurately reflect hierarchical relationships across the entire dataset.

This is illustrated schematically in Figure 10 for an OptiSim selection set of 10 compounds, with each compound being assigned to the cluster corresponding to the most similar member of the selection set. Note that the process scales intrinsically with $(N-M) \times M$ rather than scaling with N^3 , as hierarchical clustering does (N^2 where RNN⁸ can be used). Such OptiSim clustering makes it possible to compare OptiSim with other clustering methods with

respect to cluster size distributions. Figure 11 shows characteristic cluster size distributions for single linkage, group average and complete linkage methods. Note that here, "size" refers simply to membership count, not to how much of fingerprint space each cluster covers. Pyridine memberships are shown as dark bars, whereas cyclohexanes are indicated by hashed bars and pyrimidines are indicated by stippled bars. Circles indicate the location and identity of singleton clusters.

For single linkage (top), most of the pyridines (89% of the entire dataset) constitute a single large cluster, and only one other cluster of any size is found. The pyrimidines, many of the cyclohexanes and a few pyridines are spread among singletons and doubletons. The clusters obtained using group average clustering show a more useful level of resolution among the pyridines, but still discriminates too effectively among the pyrimidines. Among the methods illustrated in Figure 11, the most intuitively appropriate balance between representativeness (in this case, discriminating among pyridines) and diversity (discriminating among pyrimidines) seems to be struck by complete linkage clustering (bottom).

Figures 12 and 13 compare the cluster size distributions obtained for OptiSim clusterings based on $K = 1$ and 2 or 3 and 5, respectively. At the smaller subsample size, the clustering is representative in that the pyridines are well distributed across clusters; the uncommon compounds - here, cyclohexanes and pyrimidines - fall into just one or two clusters each. Indeed, in some cases cyclohexanes get lumped in with pyridines. As the subsample size grows, discrimination among the more distinctive compound classes increases, until at $K = 5$ (middle) the distribution is quite similar to that seen for complete linkage clustering (bottom).

There is one respect in which the OptiSim clustering for $K = 5$ differs appreciably from that for complete linkage. Note that the cyclohexane clusters are considerably more even in size in the latter case. This reflects the fact that the OptiSim clusters can and will adjust their diameters (maximum pairwise dissimilarity within the cluster) somewhat to compensate for "local" variations in scale and/or spatial distribution. This flexibility is an advantage over hierarchical methods in general and complete linkage in particular. It arises because the OptiSim selection method is inherently progressive: the first selection by definition represents the whole dataset, and subsequent selections fill in details of areas not yet adequately represented. Indeed, such progressivity is one of the desirable hallmarks of divisive clustering methods^{1,9}, which are not themselves generally well suited for application to large datasets.

Clinical Trial Design:

At present, populations for clinical trials are generally chosen to be as homogeneous as possible. This is done to maximize the sensitivity of the tests to treatment effects. Due to the recognition that subpopulations may exist, there is growing pressure to move away from this paradigm, however, and run clinical trials in more heterogeneous populations. There are several scenarios under which this becomes beneficial:

- 1) A significant subpopulation exists which reacts badly to the treatment being studied. Heritable allergies and drug interactions fall into this category.
- 2) The intended benefit is not seen in the general population, but a significant subpopulation exists for which the intended benefit is realized and is of substantial value.
- 3) There is an unanticipated benefit to the treatment, but one which is only realized in a subpopulation. Hair growth stimulators and impotence relief treatments fall into this category.
- 4) There is significant systematic variation in response to the treatment, either due to genetics (P450 or other metabolism) or because of interactions with other drugs.

All of these subpopulation effects could potentially be detected by doing clinical trials on more varied test populations. Since the relevant subpopulation will not, in general, be known ahead of time, the best approach is to create a representative diverse sample based on a large number of personal characteristics - genetic, physical, lifestyle, etc. OptiSim is ideally suited for defining an appropriate test group from such information since it allows intelligent choices to be made between the representativeness and diversity of the subsets of test populations to be chosen.

Internet Searching:

The Internet represents an immense body of information which is expanding at a phenomenal rate. A major problem presented by so much readily accessible information is the ability to find the item(s) of interest. OptiSim may be applied to Internet searching to simplify the task of identifying relevant information. At present, such searches, of necessity, operate off a hierarchy of keywords and indices. Besides the sheer volume of information which needs to be searched, this approach is susceptible to various abuses by Net publishers, some conscious and some accidental, as well as to the idiosyncracies of the various search engines and is prone to losing signal in the torrent of noise. As a result, users often have difficulty

finding the information they seek. An alternative methodology enabled by OptiSim would be to collect all addresses which might be relevant to the query, then use OptiSim to select diverse representatives and cluster the rest for perusal as appropriate. The user could by experience determine his/her personal value of K which most frequently returned information of most interest.

OptiSim is a generalized dissimilarity selection methodology which includes the established methods of maximum and minimum dissimilarity selection as special cases. By varying the subsample size K , one can adjust the balance between how representative the selected subset is and how diverse it is. Intermediate settings can mimic the results obtained for selection based on hierarchical clustering or, in some cases at least, improve upon them. Different embodiments of the invention disclosed in this document will consist of different datasets, different subset sizes, different dissimilarity measures, and different choices for the value of K . All are considered within the scope of the teaching of the OptiSim invention. In addition, those skilled in the art will recognize that various modifications, additions, substitutions, and variations to the illustrative examples set forth herein can be made without departing from the spirit of the inventions and are, therefore, considered within the scope of the invention.

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Appendix "A"

@macro TILE sybyltable

#####

globalvar TABLE!TILE!NO RAND_K TANIMOTO

```
5  localvar rowz ro_count ro_count0 ro_set keep_ct
    localvar c colz colf kept type overflow
    localvar tempz tempf K k0 R R2 i j keepers oncers
    localvar nada d df selz d_to_ks min_d max_d q trials
```

```
if %not( %table_default() )
```

```
10  echo TABLE TILE requires an open table.
```

```
    return
```

```
endif
```

```
setvar rowz $1
```

```
setvar ro_count %table( "$rowz" row count )
```

```
15  while %lteq( $ro_count 0 )
```

```
    setvar rowz %prompt( ROW_EXP "" "Rows to use" )
```

```
    if $status
```

```
        return
```

```
    endif
```

```
20  setvar ro_count %table( "$rowz" row count )
```

```
endwhile
```

```
setvar colz %table( "$2" COL NUMBER )
```

```
while %not( $colz )
```

```
    setvar colz %prompt( COL_EXP "" "Columns to Use" )
```

```
25  if $status
```

```
        return
    endif
    setvar colz %table( "$colz" COL NUMBER )
endwhile

5
setvar tempz
setvar tempf
for c in $colz
    setvar type %table( $c COLUMN DATA_TYPE )
10    if %set_member( "$type" INT,DOUBLE,FLOAT )
        switch %table( $c COLUMN COLUMN_TYPE )
            case FINGERPRINT)
            case ATOM_PAIR_FP)
                setvar tempf $tempf $c
15                ;;
            case )
                setvar tempz $tempz $c
                ;;
            endswitch
20    else
        echo "Sorry; %table( $c COL NAME ) is not suitable for this analysis."
    endif
endfor

if $tempz $tempf
25    setvar colz $tempz
    setvar colf $tempf
else
    echo No valid columns specified.
    return
30 endif
```

```
setvar K $3
while %not( %syb_int( "$k" ) )
    setvar K %prompt( NATURAL 0 "Horizon sample size" \
        "Size of sample to consider at each step; 0 tests all." )
5   if $status
        return
    endif
endwhile

setvar STATUS
10  setvar R %promptif( "$4" POSITIVE "" "Cluster Radius" \
    "Positive number specifying maximum allowed radius for bins." )
    if $status
        return
    endif
15  setvar R2 %sqr( $r )

    setvar M %promptif( "$5" POSITIVE "" "Max number of centers to identify" \
        "Enter 0 to get all possible." )
    if $status
        return
20  endif

# setvar ro_set %set_create( $rowz )
##
# Select rows then drop if there is missing data
##
25  command TABLE DELAY YES

# command TABLE SELECT ROW $ro_set
command TABLE SELECT ROW $rowz
```

```
for c in $colz
  setvar nada %cat( '{missing(' $c ')}' )
  command TABLE DESELECT ROW $nada
endfor
5  setvar rowz %table( {selected()} ROW NUMBER )
  if %not( $rowz )
    echo Sorry; no specified rows have all required data.
    return
  endif

10 #
   # Begin partitioning
   #
   ON INTERRUPT return
   #
15 # Prime the pump
   #
   setvar ro_count %table( {selected()} ROW COUNT )
   if $TABLE!TILE!NO_RAND_K
     setvar q 1
20   setvar keepers %arg( $q $rowz )
   else
     setvar q %math( ( %irand( $6 ) % $ro_count ) + 1 )
     setvar keepers %arg( $q $rowz )
     setvar nada %arg( $ro_count $rowz )
25   setvar rowz %setarg( $q "$nada" $rowz )
   endif
   setvar keep_ct 1

   setvar ro_count0 $ro_count
   setvar ro_count %math( $ro_count - 1 )
```

setvar oncers

setvar overflow

if %eq(\$k 0)

setvar k \$ro_count

5 if \$TABLE!TILE!NO_RAND_K

setvar k0 \$TABLE!TILE!NO_RAND_K

else

setvar k0 \$ro_count

endif

10 else

setvar k0 \$k

endif

if %eq(\$m 0)

setvar m \$ro_count

15 endif

XXXX

if \$tanimoto

setvar tanimoto %sqrt(%math(1 - \$r2))

endif

20 WHILE %and("%gt(\$ro_count 0)" "%gt(\$M \$keep_ct)")

setvar selz

setvar min_ds

WHILE %and("%lt(%count(\$selz) \$k0)" "%gt(\$ro_count 0)")

if %gt(\$k 0)

25 setvar q %math((%irand() % \$ro_count) + 1)

31

```
    setvar i    %arg( $q $rowz )
    setvar nada %arg( $ro_count $rowz )
    setvar rowz %setarg( $q "$nada" $rowz )
else
5  #    setvar i    %arg( $ro_count $rowz )
    setvar i    %arg( %math( $ro_count0 - $ro_count + 1 ) $rowz )
endif
setvar ro_count %math( $ro_count - 1 )

setvar try_these $keepers
10  if $animoto
    setvar card_i %rcell( $i $colf value )
    setvar try_these
    for j in $cards[ 0 ]
        setvar minT %min( %math( $card_i / $j ) %math( $j / $card_i ) )
15    if %gt( %min( $maxT $minT ) $temp_max )
        setvar try_these $try_these $cards[ $j ]
    endif
    endfor
endif

20  setvar d_to_ks
    setvar j
    for j in $try_these

        setvar d %table_tile_distance( $i $j "$colz" "$colf" )

        if %gt( $d $r2)
25    setvar d_to_ks $d_to_ks $d
        else
            break
        endfor
    endfor
```

endif

endfor

if %not(\$j)

setvar selz \$selz \$i

5 if \$d_to_ks

setvar min_ds \$min_ds %min(\$d_to_ks)

endif

endif

if %and("%lteq(\$ro_count 0)" "%gt(\$k 0)")

10 if \$oncercs

setvar rowz \$oncercs

setvar ro_count %count(\$rowz)

setvar oncers

endif

15 endif

ENDWHILE

if \$selz

setvar max_d %max(\$min_ds)

20 setvar q %array_pos("\$max_d" \$min_ds)

setvar kept %arg("\$q" \$selz)

setvar keepers \$keepers \$kept

setvar keep_ct %math(\$keep_ct + 1)

setvar selz %item_remove(\$q \$selz)

25 setvar selz %setarg(\$q "" \$selz)

```
setvar oncers $oncers $selz
```

```
if %lteq( $ro_count 0 )
```

```
    setvar rowz $oncers
```

```
    setvar ro_count %count( $rowz )
```

```
5    setvar oncers
```

```
endif
```

```
if $overflow
```

```
    echo -n "$kept is center no. %count( $keepers ) ... " \r
```

```
else
```

```
10    if %lt( %strlen( "$keepers" ) 100 )
```

```
        echo -n "Found %count( $keepers ) centers: " $keepers \r
```

```
    else
```

```
        echo
```

```
        setvar overflow TRUE
```

```
15    echo -n "$kept is center no. %count( $keepers ) ... " \r
```

```
    endif
```

```
endif
```

```
endif
```

```
ENDWHILE
```

```
20 if $keepers
```

```
    echo "Found %count( $keepers ) centers: " $keepers
```

```
    if $TABLE!TILE!NO_RANDOM_K
```

```
        echo "Accessed all but last $ro_count rows."
```

```
    endif
```

```
25 else
```

```
    echo No centers found!
```

endif

command TABLE DELAY NO

command TABLE SELECT ROW %set_create(\$keepers)

5

#####

##

Returns distance squared for use in tiling macro.

NB: \$3 and \$4 are lists, not sets, of column ids

10 ## ##

Bob Clark 10/9/96

##

#####

@expression_generator table_tile_distance

15 if %not(%gt(\$# 2))

echo 'Usage: %table_tile_distance(row_id "scalar_cols" "finger_cols")'

return

endif

localvar c d df colf colz i j

20 setvar i \$1

setvar j \$2

setvar colz \$3

setvar colf \$4

setvar d 0

```

for c in $colz
    setvar d %math( $d + %sqr( %math( %rcell( $i $c VALUE ) - %rcell( $j $c VALUE
)))
endfor
5  ##
  # Check fingerprint columns
  ##
  for c in $colf
    switch $TAILOR!SELECTOR!METRIC
10    case TANIMOTO)
      setvar df %tanimoto( $c $j $i )
      ;;
      case COSINE)
        setvar df %cosineco( $c $j $i )
15        ;;
        case EUCLIDEAN)
          # setvar df %fing_euclid( $c $j $i )
          ;;
        endswitch

20    setvar d %math( $d + %sqr( %math( 1 - $df ) ) )
    endfor

    %return( $d )

    .
    @expression_generator subset_sim

25  localvar c colz d colz i j
    localvar fingz
    localvar min_ds min_this nada oops

```

```
localvar q query_ct query_set
localvar ref_ct ref_set
localvar scalz tanz stats

setvar oops

5  if %not( %eq( $# 3 ) )
    setvar oops TRUE
else
    setvar colz      %table( "$1" col number )
    setvar ref_set   %table( "$2" row number )
10  setvar ref_ct    %count( $ref_set )
    setvar query_set $3
    setvar query_ct  %table( "$3" row count )
endif

    if %not( $ref_set )
15  setvar oops TRUE
endif

    if %lt( $query_ct 1 )
        setvar oops TRUE
    endif

20  if %neq( %count( $colz ) 1 )
        setvar oops TRUE
    endif

    if $oops
        echo 'Usage: %subset_sim( ref_rows query_rows metric_column )'
25  return
```

endif

for c in \$colz

setvar nada %cat('{missing(' \$c ')}')

setvar foo %mss_set_create(%table("\$nada" row number))

5 if \$foo

setvar query_set %mss_set_diff(\$query_set \$nada)

endif

endfor

if %not(\$query_set)

10 ERROR Too many rows have missing data

return

endif

setvar scalz

setvar fingz

15 for q in \$colz

setvar nada %table(\$colz col data)

if %not(%set_member("\$nada" DOUBLE,INT,FLOAT))

echo 'Metric column %table(\$q col name) is inappropriate; skipping...'

continue

20 endif

switch %table(\$q col column_type)

case FINGERPRINT)

case ATOM_PAIR_FP)

setvar fingz \$fingz \$q

25 ;;

case)

setvar scalz \$scalz \$q

```
;;
endswitch
endfor

setvar min_ds

5  for i in $ref_set
    setvar nada %cat( '(' "$query_set" ')' '-' $i )
    setvar q %table( $nada row number )

    if %not( $q )
        echo 'No rows to compare to ' %table( $i row name); skipping...
10    continue
    endif

    setvar min_this
    for j in $q
        setvar d %table_tile_distance( $i $j "$scalz" "$fingz" )
15    if %not( $d )
        echo No distance returned for $i $j
        continue
    endif

    if %not( $min_this )
20    setvar min_this $d
    endif

    if %lt( $d $min_this )
        setvar min_this $d
    endif
25 endfor
```



```
if $min_this
  setvar min_ds $min_ds %sqrt( $min_this )
endif
endfor
```

```
5  setvar stats %stats( $min_ds )
   %return( "$stats" )
```

@macro SUBSET_SIMILARITY CHOM

```
localvar colz nada ques refs stats
10 localvar reps divers tabx
```

```
setvar GLOBAL!STATUS
```

```
ON INTERRUPT goto flee_chom_subset_similarity
```

```
setvar tabx %table_default()
```

```
if $tabx
15  echo
    echo working table is $tabx
else
    echo No table is currently active
    return
20 endif
```

```
setvar colz %promptif( "$1" COL_EXP "{selected()}" \
  "Metric column from which to calculate (dis)similarities." )
```

```
if $global!STATUS
```

```
    return
```

```
endif
```

```
if %lt( %table( "$colz" col count ) 1 )
```

```
5    echo Sorry; expression $colz evaluates to no columns.
```

```
    return
```

```
endif
```

```
for nada in %table( $colz col data )
```

```
    if %not( %set_member( $nada DOUBLE,INT,FLOAT ) )
```

```
10    echo 'Metric column type is inappropriate for ' %table( $nada col name)
```

```
    return
```

```
    endif
```

```
endfor
```

```
setvar refs %promptif( "$2" ROW_EXP "{selected()}" \
```

```
15    "Rows to use as refernce points" )
```

```
if $global!STATUS
```

```
    return
```

```
endif
```

```
if %lt( %table( "$refs" row count ) 1 )
```

```
20    echo Sorry; expression $refs evaluates to no rows.
```

```
    return
```

```
endif
```

```
setvar ques %promptif( "$3" ROW_EXP "*" \
```

```
    "Rows for which you wish to calculate (dis)similarities." )
```

```
25 if $global!STATUS
```

```
    return
```

endif

if %lt(%table("\$ques" row count) 1)

echo Sorry; expression \$ques evaluates to no rows.

return

5 endif

setvar reps %subset_sim(\$colz \$ques \$refs)

if %not(\$reps)

echo Evaluation of intersubset similarity failed

10 return

endif

setvar divers %subset_sim(\$colz \$refs \$refs)

if %not(\$divers)

echo Evaluation of intrasubset similarity failed

15 return

endif

echo

echo " MEAN MEDIAN SD "

echo -----

20 echo "BETWEEN SETS: %printf("%10.4f %10.4f %10.4f" %arg(1 \$reps) %arg(2 \$reps
) %arg(4 \$reps))"

echo " WITHIN SET: %printf("%10.4f %10.4f %10.4f" %arg(1 \$divers) %arg(2 \$divers
) %arg(4 \$divers))"

echo

25 flee_chom_subset_similarity:

RETURN

CLAIMS

What is claimed is:

1. A computer implemented method using predetermined characteristics representative of the members of a population of selecting a member group, of predetermined size M ,
5 from the population comprising the following steps:
 - a. randomly select a member from the population, add it to the group, create a pool of candidate members out of the remainder of the population, and create an empty recycling bin;
 - b. randomly choose a member from the candidate pool and determine if it has a
10 dissimilarity less than R with respect to those members already selected for the group, and, if it does not have a dissimilarity less than R , place it in a subpopulation;
 - c. if the member selected in step b has a dissimilarity less than R to those members already selected for the group, discard that member;
 - d. repeat steps b and c until the subpopulation includes K members at least R
15 dissimilar to those already selected for the group or until the candidate pool is empty;
 - e. if the candidate pool is empty, remove all members from the recycling bin and put them into the candidate pool;
 - f. if the candidate pool is not empty, and, if there are fewer than K members in the subpopulation, go to step b;
 - g. if the subpopulation is empty, terminate the selection process;
 - h. if the subpopulation is not empty, examine the subpopulation and identify a member maximally dissimilar to those members already selected for the group;
 - i. add the member identified in step h to the group and remove it from the
25 subpopulation;
 - j. put those members in the subpopulation, which were not added to the group, into the recycling bin; and
 - k. if the desired selected group size M has been reached, terminate the selection
30 process;

1. if the desired selected group size M has not been reached, return to step b wherein the value of K is selected to determine the representativeness or diversity desired in the subset and the value of R is selected to determine the minimum dissimilarity between members.
- 5 2. The method of claim 1 in which at step j , the members are not put into the recycling bin, but rather are immediately put back into the candidate pool.
3. A computer implemented method, using predetermined characteristics representative of the members of a population, of selecting a member group, of predetermined size M , from the population comprising the following steps:
 - 10 a. randomly select a member from the population and add it to the group;
 - b. for each additional member to be included in the group, randomly create a non-redundant subpopulation from the whole population;
 - c. select, using a preference criterion, the member from the subpopulation which best satisfies the preference criterion with respect to those members already
15 selected for inclusion in the group;
 - d. repeat steps a and b until M members are selected or until a non-redundant subpopulation can not be obtained.
4. The method of claim 3 in which the subpopulation size is varied to adjust the representativeness or diversity of the group.
- 20 5. A computer implemented method, using predetermined characteristics representative of the members of a population, of selecting a member group, of predetermined size M , from the population comprising drawing the members for testing for inclusion in the group from a subpopulation the size of which is varied to balance the representativeness and diversity of the members selected.
- 25 6. The method of claim 5 in which the subpopulation is randomly selected and non-redundant.
7. The method of claim 5 in which the testing of the members for inclusion in the group comprises satisfying a preference criterion.
8. The method of claim 5 utilizing subpopulations of size K , where K is not equal to 1,
30 in which the number of iterations necessary to select the group is less than or equal to the population size and typically equals the square root of the population size.

9. A computer implemented method, using predetermined characteristics representative of the members of a population, of selecting a member group, of predetermined size M , from the population comprising utilizing subpopulations of size K , where K is not equal to 1, in which the number of iterations necessary to select the subset is less than or equal to the population size and typically equals the square root of the population size.
- 5
10. The group of members selected, using predetermined characteristics representative of the members of a population, from a larger population by the method comprising the following steps:
- 10
- a. randomly select a member from the population, add it to the group, create a pool of candidate members out of the remainder of the population, and create an empty recycling bin;
- b. randomly choose a member from the candidate pool and determine if it has a dissimilarity less than R with respect to those members already selected for the group, and, if it does not have a dissimilarity less than R , place it in a subpopulation;
- 15
- c. if the member selected in step b has a dissimilarity less than R to those members already selected for the group, discard that member;
- d. repeat steps b and c until the subpopulation includes K members at least R dissimilar to those already selected for the group or until the candidate pool is empty;
- 20
- e. if the candidate pool is empty, remove all members from the recycling bin and put them into the candidate pool;
- f. if the candidate pool is not empty, and, if there are fewer than K members in the subpopulation, go to step b;
- 25
- g. if the subpopulation is empty, terminate the selection process;
- h. if the subpopulation is not empty, examine the subpopulation and identify a member maximally dissimilar to those members already selected for the group;
- i. add the member identified in step h to the group and remove it from the subpopulation;
- 30
- j. put those members in the subpopulation, which were not added to the group,

into the recycling bin; and

k. if the desired selected group size M has been reached, terminate the selection process;

l. if the desired selected group size M has not been reached, return to step b

5 wherein the value of K is selected to determine the representativeness or diversity desired in the subset and the value of R is selected to determine the minimum dissimilarity between members.

11. The group of members selected, using predetermined characteristics representative of the members of a population, from a larger population by the method comprising the
10 following steps:

a. randomly select a member from the population and add it to the group;

b. for each additional member to be included in the group, randomly create a non-redundant subpopulation from the whole population;

15 c. select, using a preference criterion, the member from the subpopulation which best satisfies the preference criterion with respect to those members already selected for inclusion in the group;

d. repeat steps a and b until M members are selected or until a non-redundant subpopulation can not be obtained.

12. The group of members of claim 11 in which the subpopulation size is varied to adjust
20 the representativeness or diversity of the group.

13. The group of members selected, using predetermined characteristics representative of the members of a population, from a larger population by the method comprising drawing the members for testing for inclusion in the group from a subpopulation the size of which is varied to balance the representativeness and diversity of the members
25 selected.

14. The group of members selected, using predetermined characteristics representative of the members of a population, from a larger population by the method comprising utilizing subpopulations of size K , where K is not equal to 1, in which the number of iterations necessary to select the subset is less than or equal to N and typically equals
30 the square root of N .

15. A computer implemented method for clustering members of a large population, using

predetermined characteristics representative of the members of a population, in which the center of the clusters to be formed are determined by the groups selected from the population by the method comprising the following steps:

- a. randomly select a member from the population, add it to the group, create a pool of candidate members out of the remainder of the population, and create an empty recycling bin;
- b. randomly choose a member from the candidate pool and determine if it has a dissimilarity less than R with respect to those members already selected for the group, and, if it does not have a dissimilarity less than R , place it in a subpopulation;
- c. if the member selected in step b has a dissimilarity less than R to those members already selected for the group, discard that member;
- d. repeat steps b and c until the subpopulation includes K members at least R dissimilar to those already selected for the group or until the candidate pool is empty;
- e. if the candidate pool is empty, remove all members from the recycling bin and put them into the candidate pool;
- f. if the candidate pool is not empty, and, if there are fewer than K members in the subpopulation, go to step b;
- g. if the subpopulation is empty, terminate the selection process;
- h. if the subpopulation is not empty, examine the subpopulation and identify a member maximally dissimilar to those members already selected for the group;
- i. add the member identified in step h to the group and remove it from the subpopulation;
- j. put those members in the subpopulation, which were not added to the group, into the recycling bin; and
- k. if the desired selected group size M has been reached, terminate the selection process;
- l. if the desired selected group size M has not been reached, return to step b

wherein the value of K is selected to determine the representativeness or diversity desired in the subset and the value of R is selected to determine the minimum dissimilarity between

members.

- 5 16. A computer implemented method for clustering members of a large population, using predetermined characteristics representative of the members of a population, in which the center of the clusters to be formed are determined by the groups selected from the population by the method comprising the following steps:
- a. randomly select a member from the population and add it to the group;
 - b. for each additional member to be included in the group, randomly create a non-redundant subpopulation from the whole population;
 - 10 c. select, using a preference criterion, the member from the subpopulation which best satisfies the preference criterion with respect to those members already selected for inclusion in the group;
 - d. repeat steps a and b until *M* members are selected or until a non-redundant subpopulation can not be obtained.
- 15 17. The method of claim 1 in which the predetermined characteristic representative of the members of the population is chemical structure.
18. The method of claim 3 in which the predetermined characteristic representative of the members of the population is chemical structure.
19. The method of claim 5 in which the predetermined characteristic representative of the members of the population is chemical structure.
- 20 20. The method of claim 9 in which the predetermined characteristic representative of the members of the population is chemical structure.
21. The method of claim 15 in which the predetermined characteristic representative of the members of the population is chemical structure.
- 25 22. The method of claim 16 in which the predetermined characteristic representative of the members of the population is chemical structure.

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Optimal Dissimilarity at Work

$K = 5$, $R = 6$ mm, $M = 4$

FIGURE 1

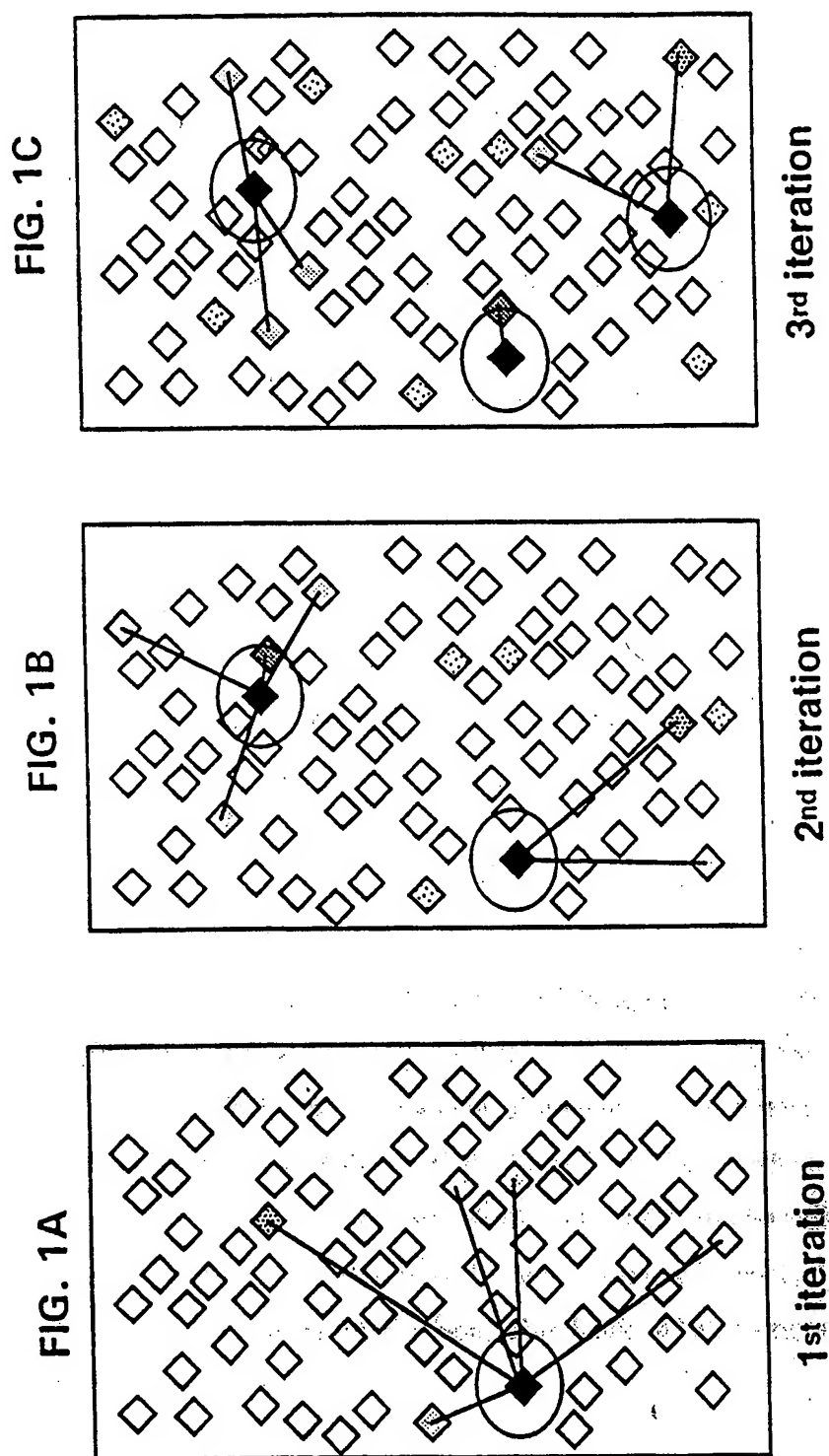


FIGURE 2

FIG. 2A

⇒ 2244 compounds

R1	R2	R3
H	F	F
F	Br	Cl
Cl	NO ₂	iPr
Br	Et	CF ₃
NO ₂	CF ₃	NMe ₂
Me	NMe ₂	SMe
Et	Ac	Ac
iPr	COCF ₃	COCF ₃
CF ₃	SPh	Ph
	OPh	SPh
	CH ₂ Ph	OPh
		CH ₂ Ph

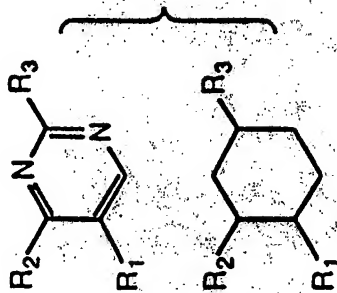
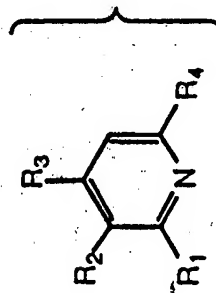


FIG. 2B

⇒ 6000 compounds

R1	R2	R3	R4
F	F	CN	F
Br	Cl	CF ₃	iPr
NO ₂	Me	Ac	CF ₃
Et	Et	COCF ₃	SMe
NMe ₂	CF ₃	CO ₂ Me	Ac
Ac	COCF ₃	CONH ₂	COCF ₃
COCF ₃	SMe		Ph
SPh	Ph		SPh
OPh	OPh		OPh
CH ₂	CH ₂ Ph		CH ₂ Ph



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FIGURE 3

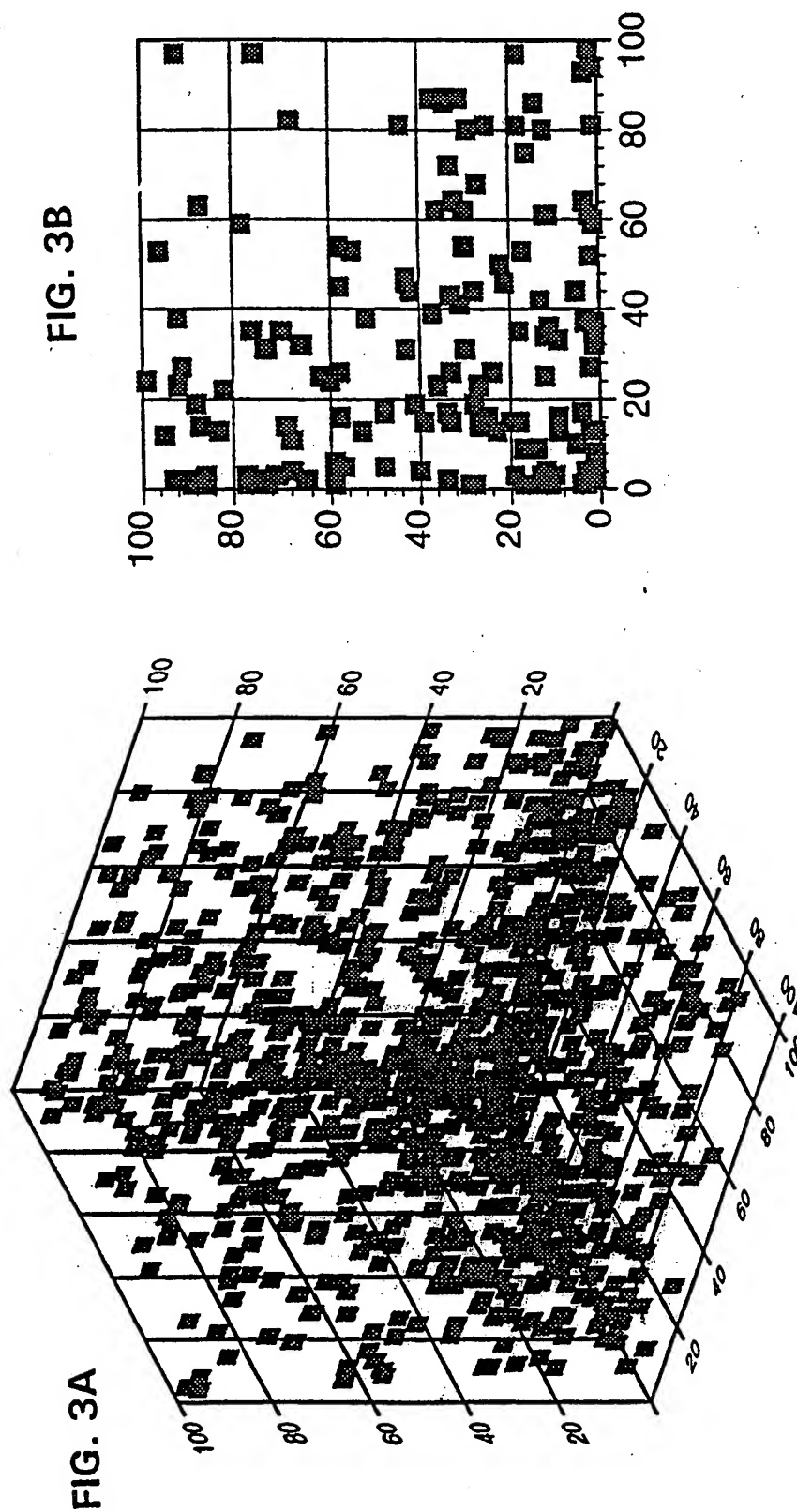
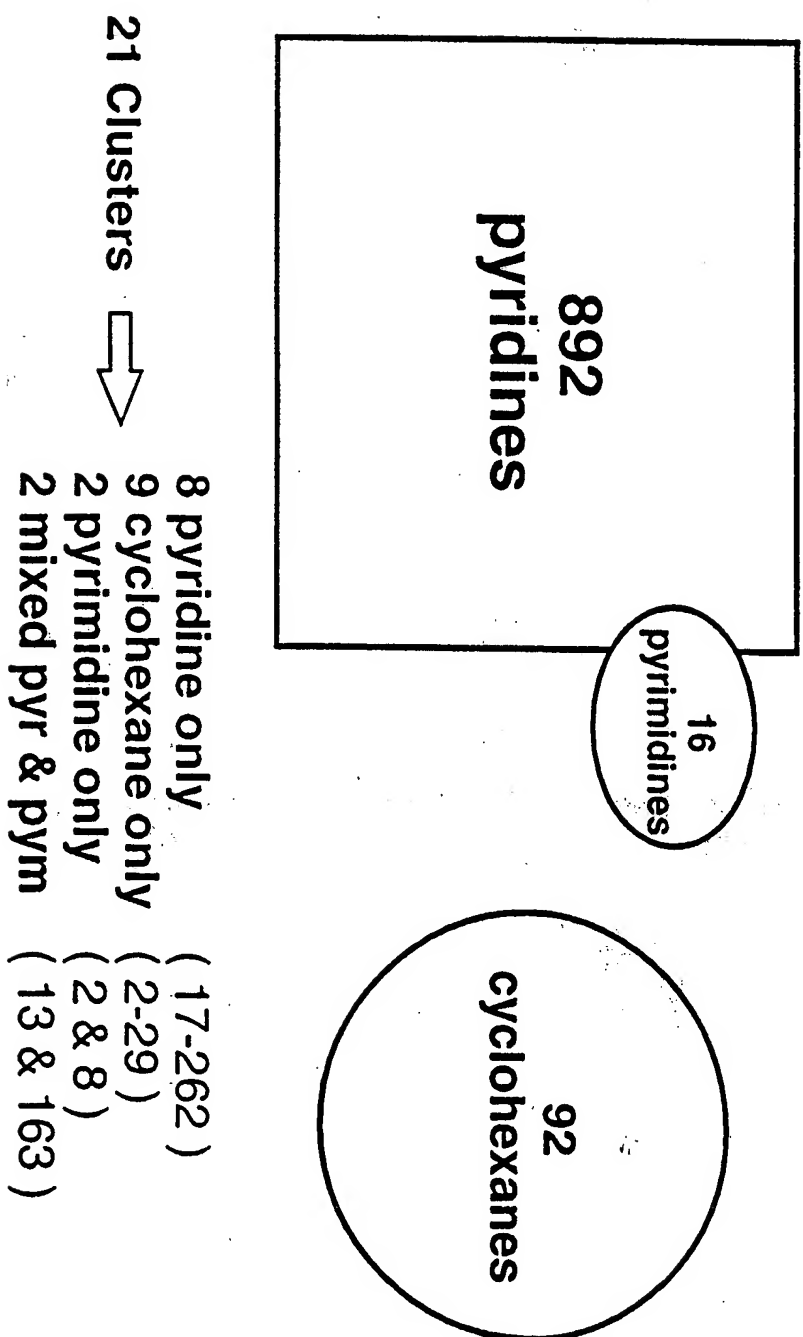
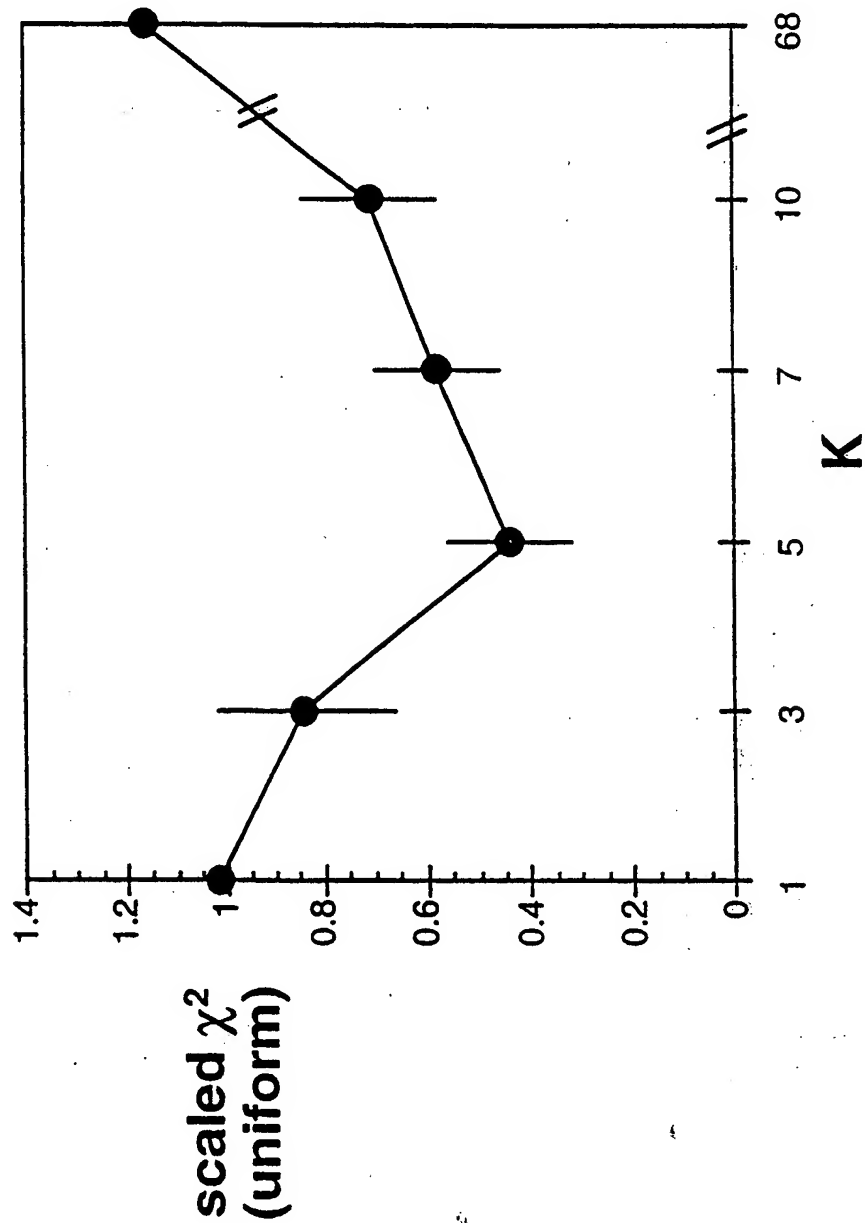


FIGURE 4



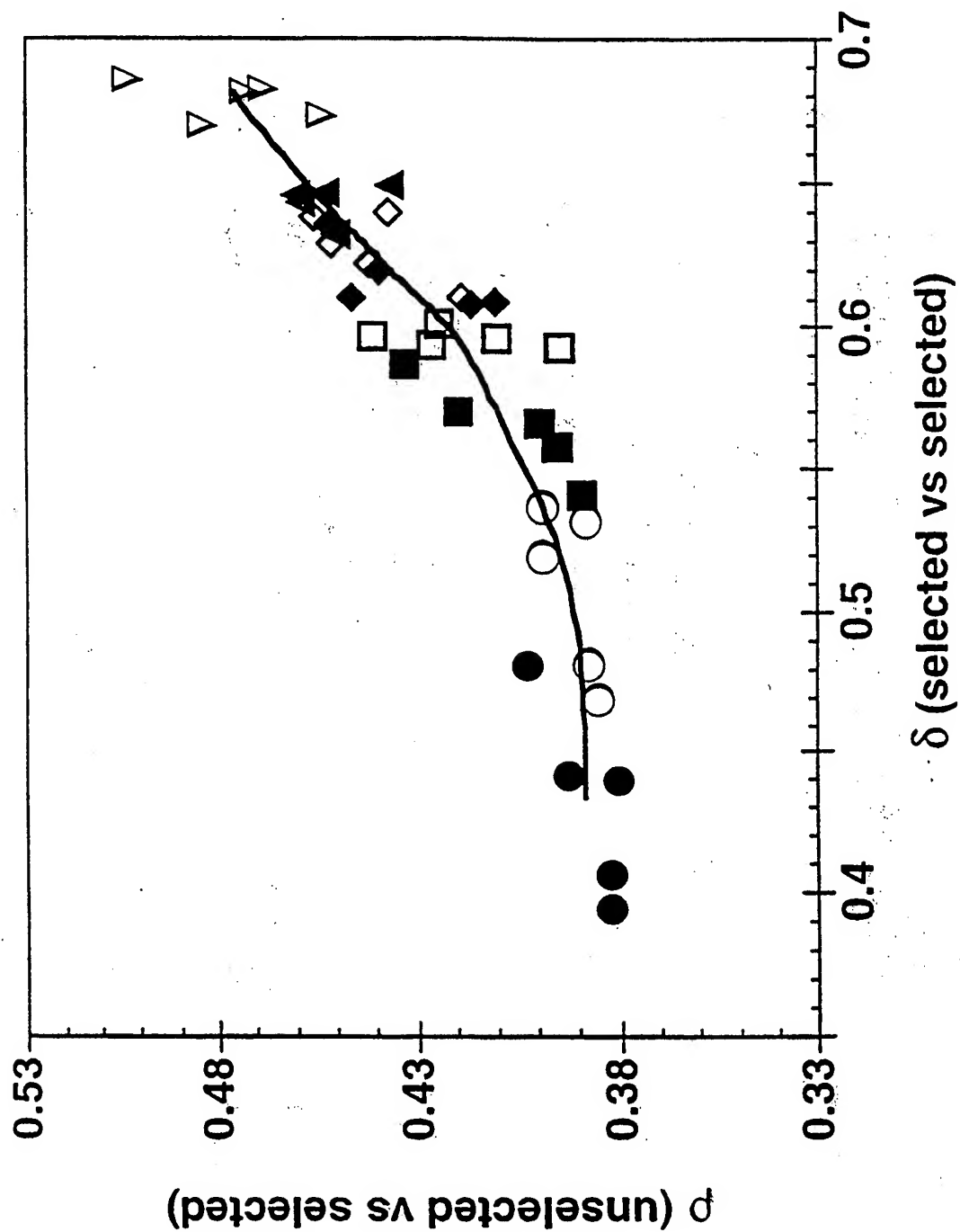
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FIGURE 5



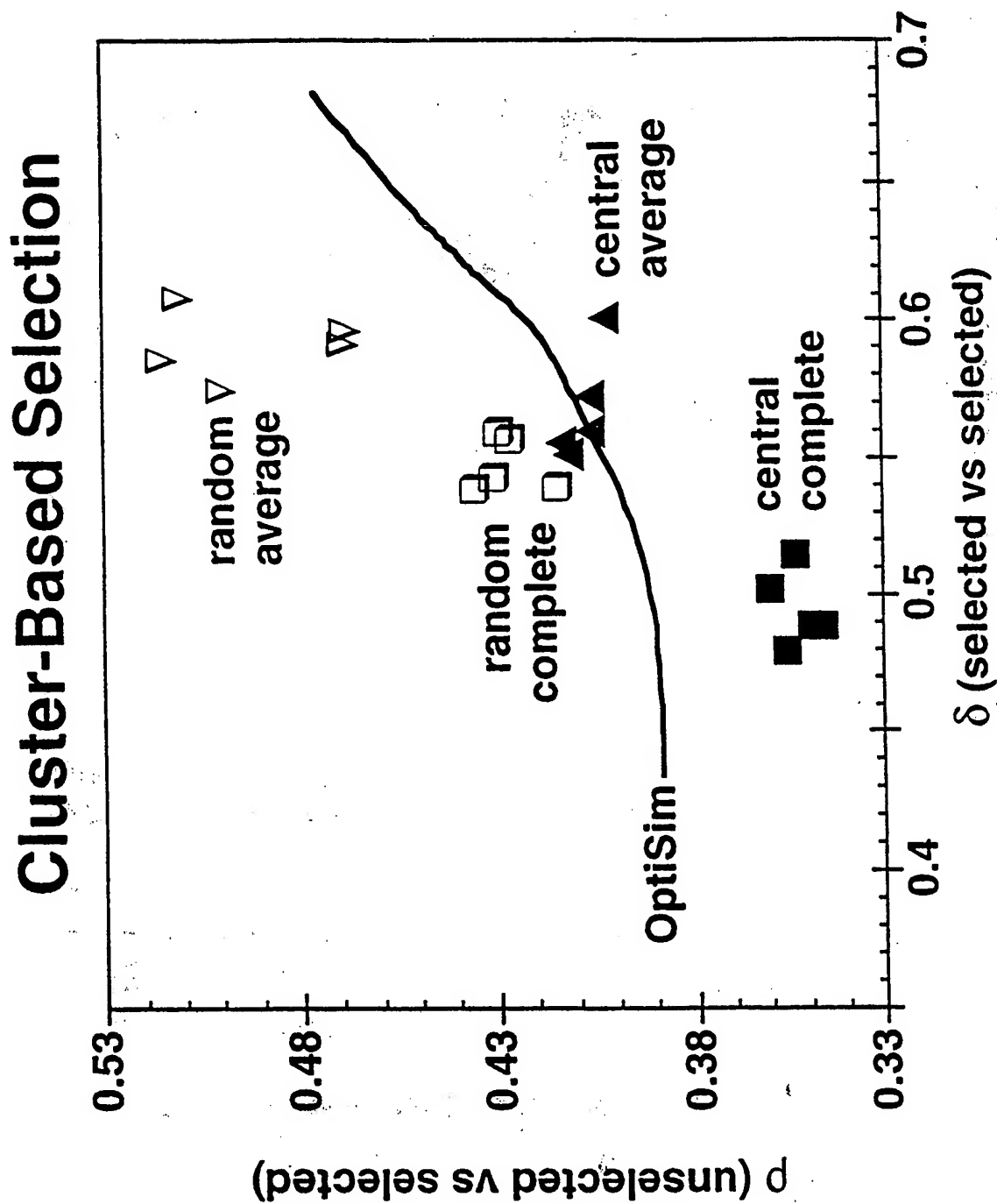
OptiSim Selection

FIG. 6A

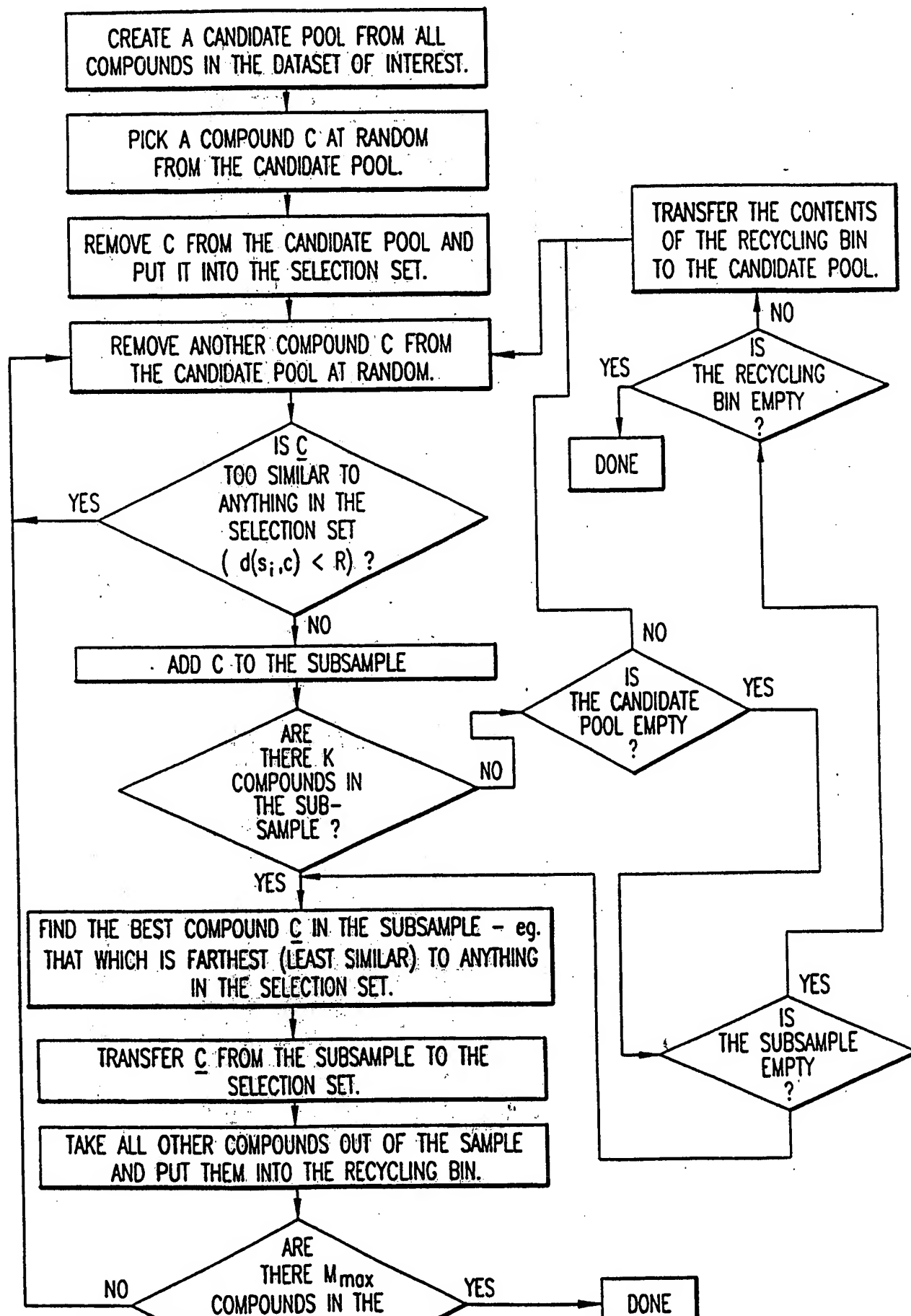


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FIG. 6B



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FIGURE 8

FIG. 8A

Single Linkage

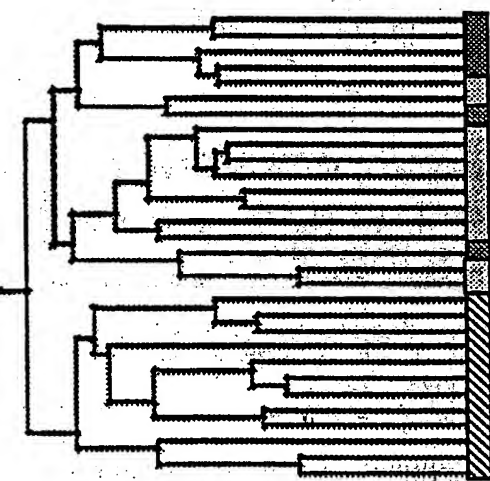


FIG. 8B

Group Average

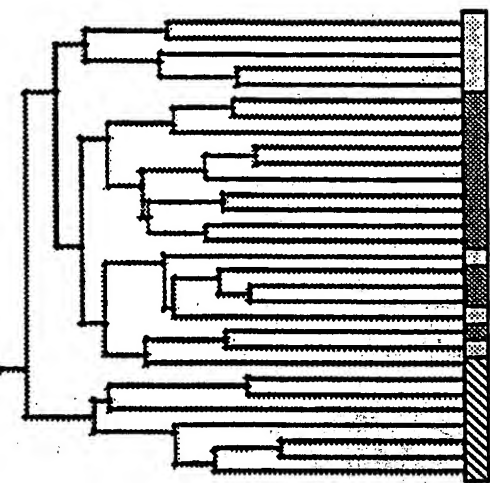
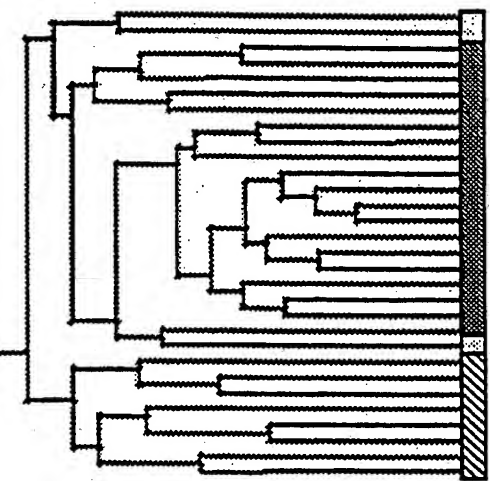


FIG. 8C

Complete Linkage

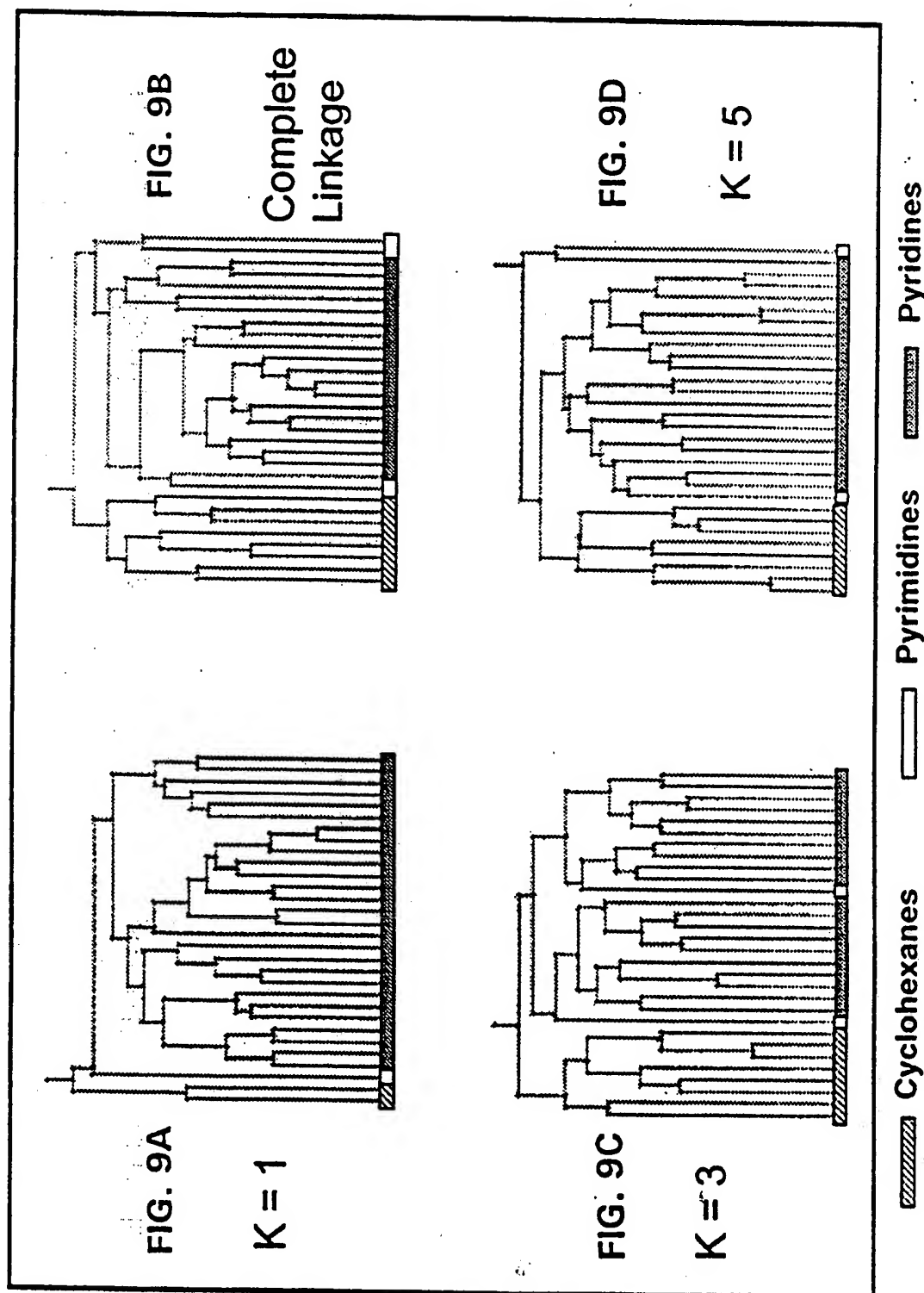


 Cyclohexanes

 Pyrimidines

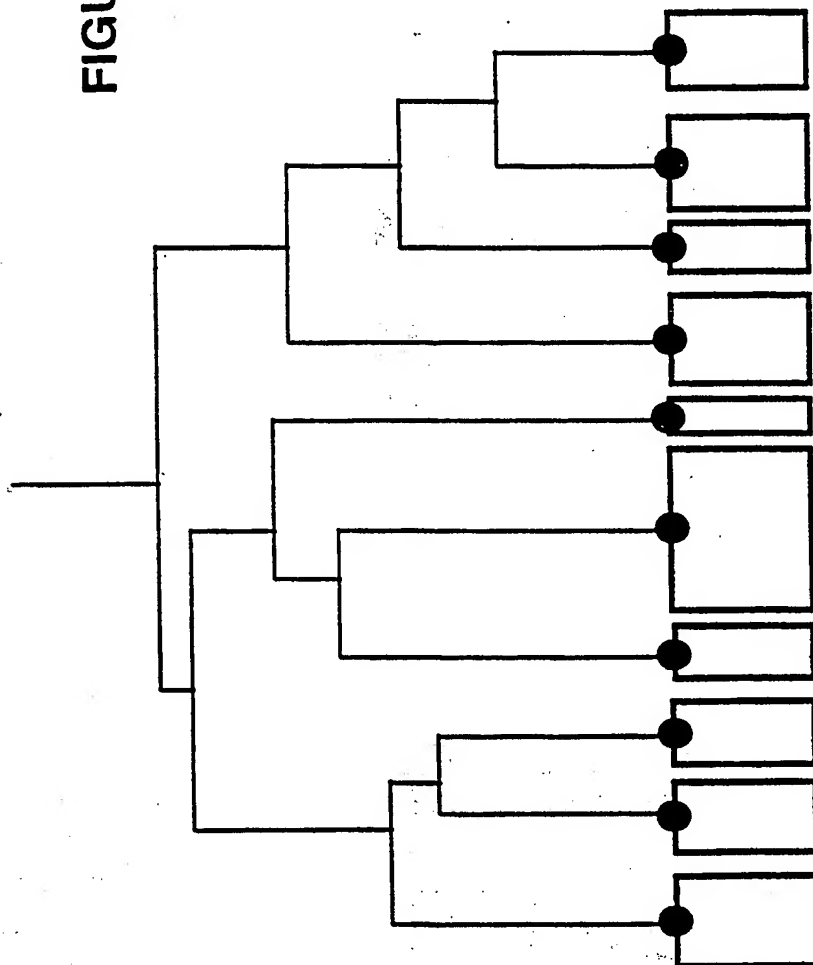
 Pyridines

FIGURE 9



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FIGURE 10



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FIGURE 11

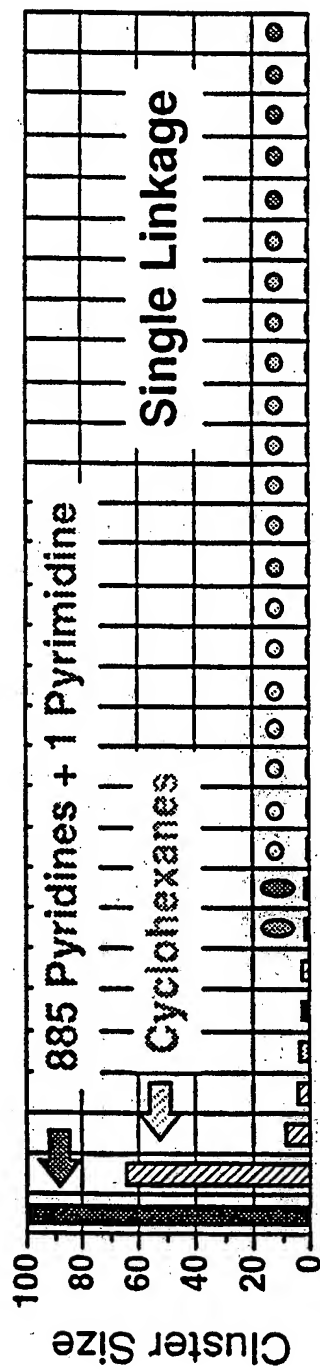


FIG. 11A

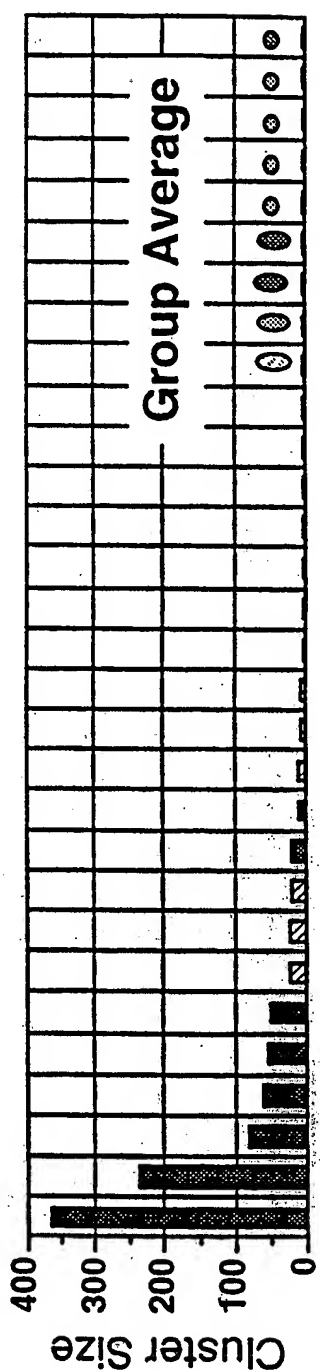


FIG. 11B

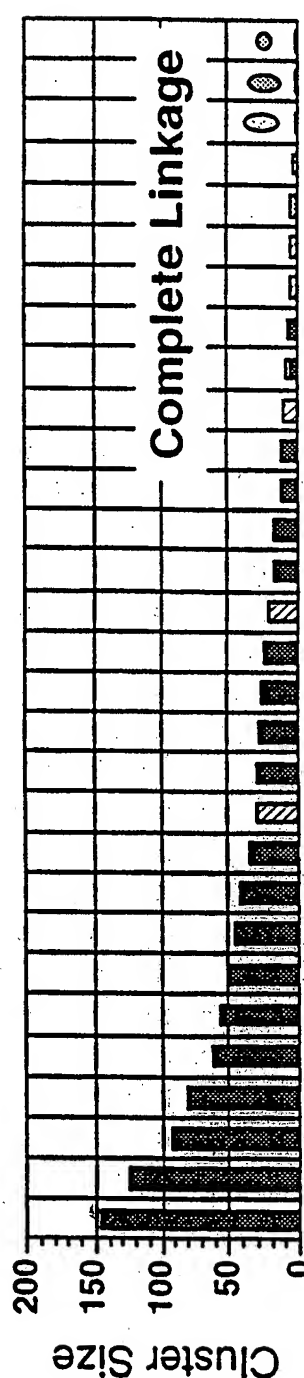
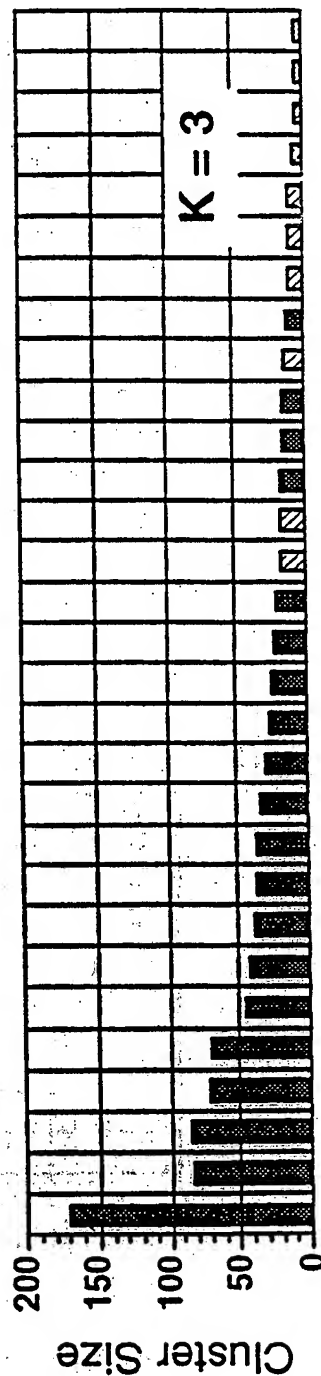
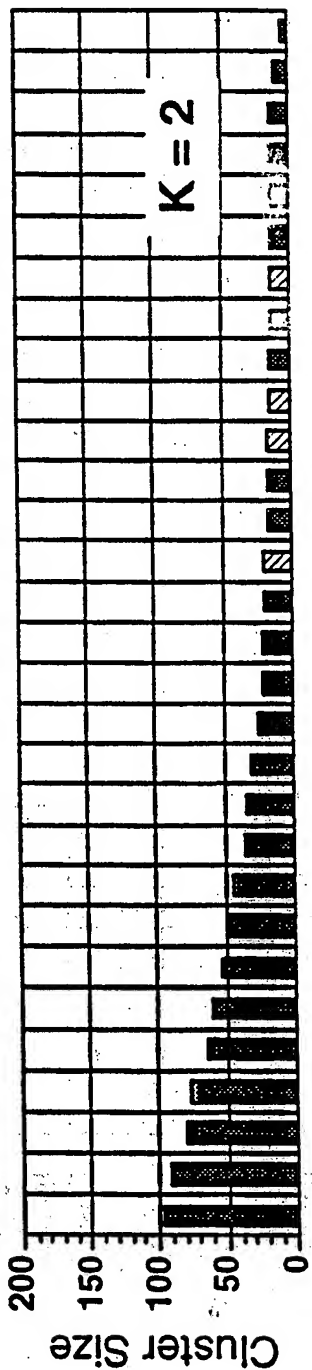
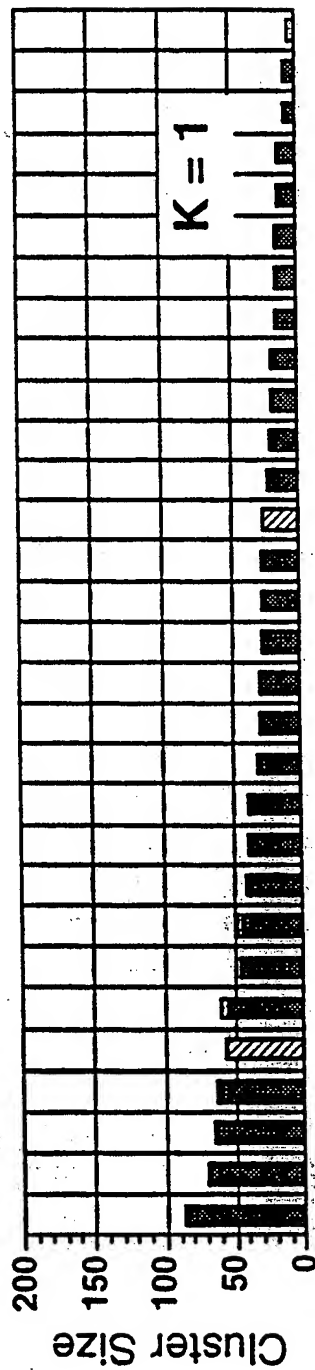


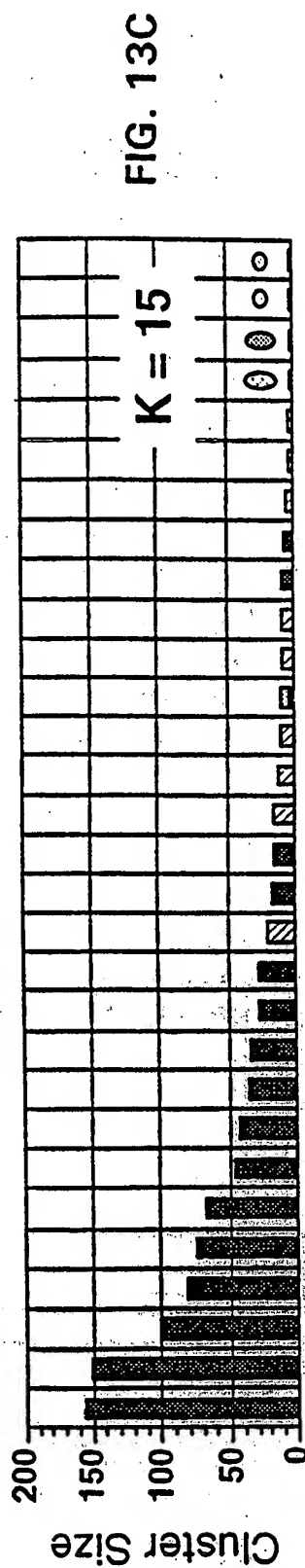
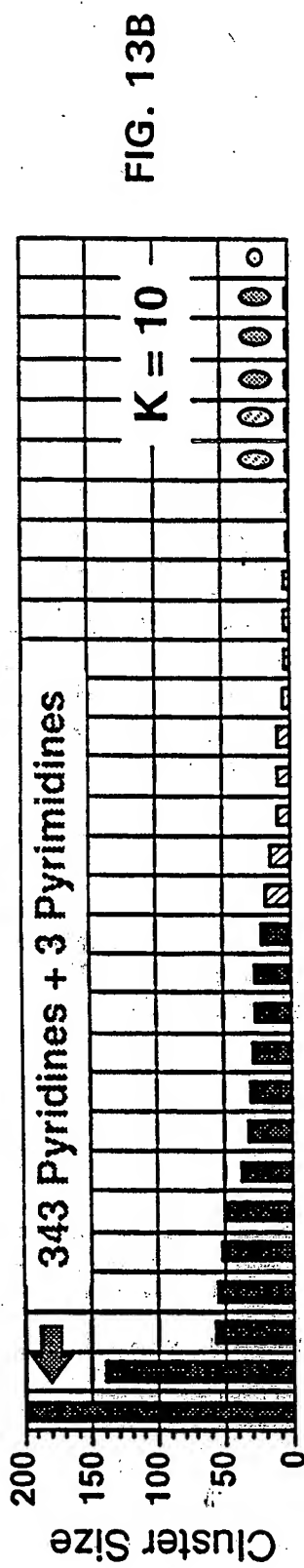
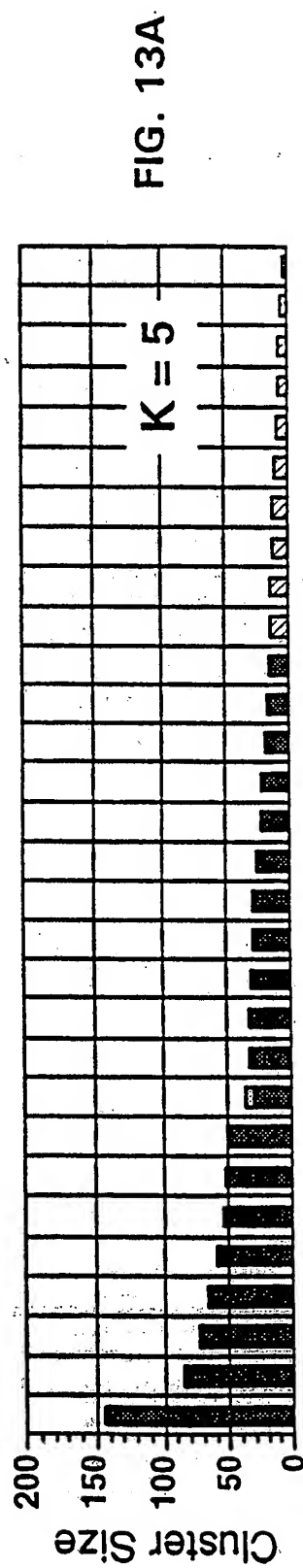
FIG. 11C

FIGURE 12



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FIGURE 13



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/07214

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : G01N 33/53; G06F 15/00, 17/00; G06G 7/58

US CL : 395/10; 435/7.1; 364/496

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 395/10; 435/7.1; 364/496

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, Dialog

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	US 5,703,792 A (D. CHAPMAN) 30 December 1997 (30/12/97), see entire document, especially column 2, line 14 to column 3, line 16. Note that no minimum dissimilarity is required and the use of a subset of candidates is not taught, only a subset of conformations of candidates (column 3 lines 8-16).	1-22
A	LANCE et al. A general theory of classificatory sorting strategies 1. Hierarchical systems. Comput J. 1967, Vol.9, pages 373-380.	1-22
A	LAJINESS et al. QSAR: Quantitative Structure-Activity Relationships in Drug Design. New York: Alan R. Liss Inc. 1989, pages 173-176, see entire document.	1-22

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/07214

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	Clark, R.D. OptiSim: An extended dissimilarity method for finding diverse representative subsets. J. Chem. Inf. Comp. Sci. November 1997, Vol.37, No.6, pages 1187-1188, see entire document.	1-22
A	Brown et al. Use of Structure-Activity Data to Compare Structure-Based Clustering Methods and Descriptors for Use in Compound Selection. J. Chem. Inf. Comp. Sci. May 1996, Vol.36, No.3, pages 572-584, see entire document.	1-22
A	BARNARD et al. Clustering of Chemical Structures on the Basis of Two-Dimensional Similarity Measures. J. Chem. Inf. Comput. Sci. November 1992, Vol.32, No.6, pages 644-649, see entire document.	1-22
A	MARTIN et al. Measuring Diversity: Experimental Design of Combinatorial Libraries for Drug Discovery. J. Med. Chem. 28 April 1995, Vol.38, No.9, pages 1431-1436, see entire document.	1-22
A	PATTERSON et al. Neighborhood Behavior: A Useful Concept for Validation of "Molecular Diversity" Descriptors. J. Med. Chem. 02 August 1996, Vol.39, No.16, pages 3049-3059, see entire document.	1-22

